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Functional competency of lower limb musculature in the elderly

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Abstract (German)

Körperlich aktiv zu sein ist Grundlage unseres täglichen Lebens. Für alle diese Aktivitäten ist das kontinuierliche Zusammenspiel des senso-motorischen System (SMS) erforderlich. Die Kontrolle der verschiedenen afferenten und efferenten Subsysteme innerhalb des SMS basiert auf Feedback-Mechanismen, die die Aufrechterhaltung des Gleichgewichts und der Stabilität während den verschiedensten statischen als auch dynamischen Aktivitäten ermöglichen. Trotz dieser Kontroll- und Stabilisierungssystems ist das kinematische und kinetische Resultat nicht konstant; stattdessen ist bei globalen „Ganzkörper-Bewegungen", und lokaler Muskelanspannung ständig eine gewisse Variabilität vorhanden.

Die Interpretation dieser Variabilität bei Bewegungshandlungen ist kontrovers. Wobei große Variabilität ist nicht zwangsläufig ein Indikator für Defizite des SMS darstellt. Das Ziel dieser Dissertation war, die Variabilität bei lokalen und globalen Bewegungshandlungen in statischen und dynamischen Ausgangstellungen zu quantifizieren. Darüberhinaus, wurde der Zusammenhang zwischen lokaler Variabilität der Muskelkraftproduktion und der Variabilität bei globalen Bewegungshandlungen.

Die Ergebnisse zeigen, dass lokale und globale Variabilität von Bewegungshandlungen in Menge und Muster verändert sind, nach Störung des SMS durch: Ermüdung, Veränderungen der Umfeldbedingungen, Alterung und bei Personen mit Sturzerfahrung. Außerdem wurde gezeigt, dass sowohl zu große als auch zu kleine Variabilität, ein entscheidendes funktionelles Defizit bei älteren Personen darstellt.

Dieser Dissertation hebt die Bedeutung der Variabilität während wiederholter Bewegungshandlungen hervor, welche einen funktionellen Biomarker für die Beurteilung von Bewegungsstörungen darstellt. In der klinische Praxis könnte dieser helfen bei der frühen Identifikation von Personen mit Bewegungsstörungen, zur Entwicklung von individual-spezifischen Rehabilitationsmaßnahmen, sowie der Beurteilung verschiedener Therapieansätze.

Kraftfluktuationen, Posturale Stabilität, Variabilität im Gang, Gang Stabilität, Power Spektrum

Abstract (English)

Undertaking activities is fundamental throughout daily living. In order to successfully perform these activities, continuous involvement of the human sensori-motor system (HSMS) is required. The HSMS involves feedback mechanisms to control numerous afferent and the efferent subsystems to ensure maintenance of balance and stability during both static and dynamic activities. Despite such control and stabilizing mechanisms, the kinematic and kinetic output of a task is not constant; instead variability occurs during continuous performance of both global tasks such as standing and walking, as well as local force production.

The interpretation of variability during output task performance remains controversial, with larger levels of variability not always indicating deficits in human-motor performance. The aim of this dissertation was to assess variability during local as well as global task performance in static and dynamic settings. Furthermore, the association between the level of variability during local force production and variability during global tasks such as standing and walking was also investigated.

The results within this dissertation showed that variability during task performance is modified in magnitude as well as in structure after perturbation due to fatigue, changes in environmental conditions, and aging, as well as in fall-prone elderly individuals. Furthermore, both high as well as low levels of variation constitute a key functional deficit among elderly individuals.

This dissertation highlights the importance of considering trial-to-trial variations during continuous task performance as a key functional biomarker for motor-related pathologies. Effective assessment of such measures of variability in clinical settings could effectively complement current clinical practice for both early and effective identification of individuals with motor-related pathology, designing subject-specific rehabilitation programs, and evaluating therapy efficacy.

Force fluctuations, postural stability, gait variability, gait stability, power spectrum, neuromuscular noise

Dedication

to mum and dad

Acknowledgement

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1. General Introduction

1.1 Background

1.1.1 Activities of daily living and increasing proportion of elderly population

The effective and successful performance of activities and tasks is the foundation of independent living. These tasks might range from relatively simple activities such as sitting, standing or drinking a cup of coffee, to complex activities that require timing, coordination and balance such as mountain climbing or snowboarding. The ability to change the location or posture, provide humans the possibility to perform activities that are essential towards living freely.

Perturbations, injuries and illnesses are all a normal components of daily living that challenge, the ever increasing proportion of elderly individuals in societies all across the world [1,2,3]. According to recent census reports in almost every western society, the proportion of people aged 65 and above was more than 13% of the entire population [1,2,3]. Furthermore, these numbers are predicted to increase by staggering amounts over the next 30-40 years due to the so-called “baby boomers” generation now entering this age group [1,2,3]. The impact of an aging society is widespread, including increasing health care and insurance costs, aging workforce (increase in the age of retirement), increase in funds needed to support pensions and/or 401k plans, as well as the propensity of people in this age-group towards injuries and illnesses. For example, elderly individuals not only are more likely to fall [4,5,6,7,8], and undergo associated injuries as well as fatalities [9,10,11], but are also vulnerable to other movement related disorders such as Parkinson’s disease, dystonia, and dementia [12,13,14,15,16]. Reliable and widespread methods for evaluation of task related outcomes within geriatric and fall-prone populations are therefore essential not only for identification of system related deficits, but also for effective implementation of preventive strategies.

1.1.2 Quantification of task performance and functioning of the human sensorimotor system

During performance of tasks and activities of daily living, irrespective of their complexity, the human sensorimotor system (HSMS) receives afferent inputs, which not only allow evaluation of the current state of the body with respect to the particular environment, but also feed this information to the efferent system. The motor or efferent system then uses this information to generate commands and actions that are necessary to accomplish the task while maintaining the relevant boundary conditions. In order to effectively perform a task, the HSMS therefore acts primarily as a feedback control system, continuously accounting for the type and quality of 1) sensory inputs (visual or somatosensory) [17,18,19,20], 2) task to be performed (static, dynamic, goal-oriented) [21,22,23,24,25,26,27], and 3) the environment (altitude, etc.) [17,20,24,25,26,27,28,29,30]. For example, the system is constantly challenged by ever-changing external factors, such as changes in the quality or the availability of visual inputs [31,32,33,34,35] or variations in the surface conditions [36]. In addition to the external conditions, however the system also has to compensate for internal or systemic characteristics, such as the level of fatigue [37,38,39], age [40,41,42,43], the presence of noise in the neuro-motor system [25,44,45,46,47,48] and pathology. The quantification of task performance outcomes after manipulating one or more of these characteristics has helped researchers and clinicians to better understand the functioning of the sensorimotor system, as well as design rehabilitation programs to improve the sensorimotor related deficits.

One such intrinsic characteristic of the sensorimotor system is the *noise* in the system, which not only hinders the accurate generation of forces, but also influences the performance of the intended movement trajectories [27,30,46,47,49,50]. Noise in the neuromuscular system can be considered as disturbances that obscure the desired output of the sensorimotor system [51]. Due to the presence of such noise, it is normal for repetitive task performance to vary around an average outcome. An example of such a phenomenon can easily be observed during submaximal isometric force production tasks. During such contractions, the muscles are unable to generate purely constant forces [22,35,52] and fluctuations in the resulting output are observed. Due to the static nature of the task, the fluctuations of force around the mean or target value closely represent the *neuromuscular noise*. Numerous studies in the past have evaluated the neuromuscular noise during such tasks to gain an understanding of various properties of the motor system including the recruitment of muscle motor units (MMUs) [22,52,53,54], the rate of discharge of action potentials [54,55,56,57,58,59], and the magnitude of the noise and its dependence on the signal [28,30,47,48] or the generation of twitch contraction [22,52,59,60,61,62]. These investigations have also formed the basis for predicting outcomes during task performance on a whole-body level [47,50]. For example, neuromuscular noise manifests itself in outcomes from both static as well as dynamic whole-body tasks [63,64]. One of the primary foci of research in recent times therefore has been the assessment of the sensorimotor system based upon the quantification of within-subject variability, or trial-to-trial variations, in the outcome of a variety of motor tasks performed by a particular individual [13,22,25,27,65]. The notion here is that such variations during multiple repetitions of a specific trial are not stochastic or random, but are a result of both the behavior and the limitations of the HSMS, in the presence as well as the absence of perturbations.

The magnitude of the variability during a particular task can be quantified either in absolute (standard deviation, SD) or relative (coefficient of variation, CV) terms of the respective units of e.g. force, acceleration, position, or time. In fact SD and CV of force during isometric force production has been used to demonstrate some of the important properties of the motor system. For example, earlier reports illustrated a linear signal-to-noise relationship using isometric force generation tasks by quantifying the magnitude of fluctuations at different effort levels [46]. Thus, the larger the magnitude of force produced, the larger the level of fluctuations present in the force output. The property of signal-dependence of noise is among one of primary reasons for researchers to assess noise (or variability) present in various task outcomes [46]. In the past, both SD and CV of center-of-pressure trajectories during quiet standing [18,19,31,65,66,67] as well as temporal gait parameters such as stride, swing and stance [13,14,40,68,69,70] have been indirectly associated with maintaining stability during standing as well as walking. The relationship between the variability in task outcome over longer durations or repetitive performance therefore provides valuable clues concerning the behavior and the characteristics of inherent task performance. Finally, as force fluctuations closely represent noise in the motor output [46,47,48,58,71], differences in the magnitude of these fluctuations after inducing perturbations (both external as well as internal such as fatigue or age) during force production tasks could provide subject-specific information that is key towards identifying or diagnosing individuals with motor-related pathologies in a clinical setting.

1.1.3 Voluntary contractions and production of force

During force production tasks, the muscle motor units (MMUs) act as transducers that convert the synaptic input received by the muscle fibers into a contractile force [22,72]. Important factors that affect this conversion include type of task, the force required, and the number as well as the type of muscle fibers and MMUs that comprise the particular muscle [52]. For example, the small muscles of the hand are organized such that all of the MMUs are activated at low thresholds in order to perform the fine motor tasks, whereas MMUs in larger muscles of e.g. the lower extremity are organized to generate a broader range of force levels that are required during standing, walking or running [54]. Regardless of the type of task and the muscle group, during any voluntary contraction, the activation of MMUs in a particular pool occurs according to the size principle [73][1]. The principle states that MMUs are recruited in a sequential manner from the smallest to the largest units that comprise the particular muscle. In other words, MMUs are recruited to produce a certain force in ascending order of their intrinsic force production capacities. A particular MMU is generally recruited when the available excitatory drive is greater than or equal to its recruitment threshold. As per the requirement of the task (or force), the magnitude of the force can be varied by either altering the number of MMUs that are activated or by modulating the action-potentials that activate the MMUs [54]. The level of synaptic input, determined by the task/force requirement, provides the net excitation (excitatory drive) available to the MMUs during voluntary contractions.

One of the most important features of the MMU pool affecting the conversion of synaptic input into force during voluntary contractions is that, in general, there are a large number of MMUs producing small forces and relatively small amount of MMUs producing large forces [74]. Based on this characteristic, Fuglevand and co-workers [54] presented a simulation model, which effectively summarized the basic rules and features that guide the conversion of synaptic input to the MMU pool into the generation of force, using the following equation:

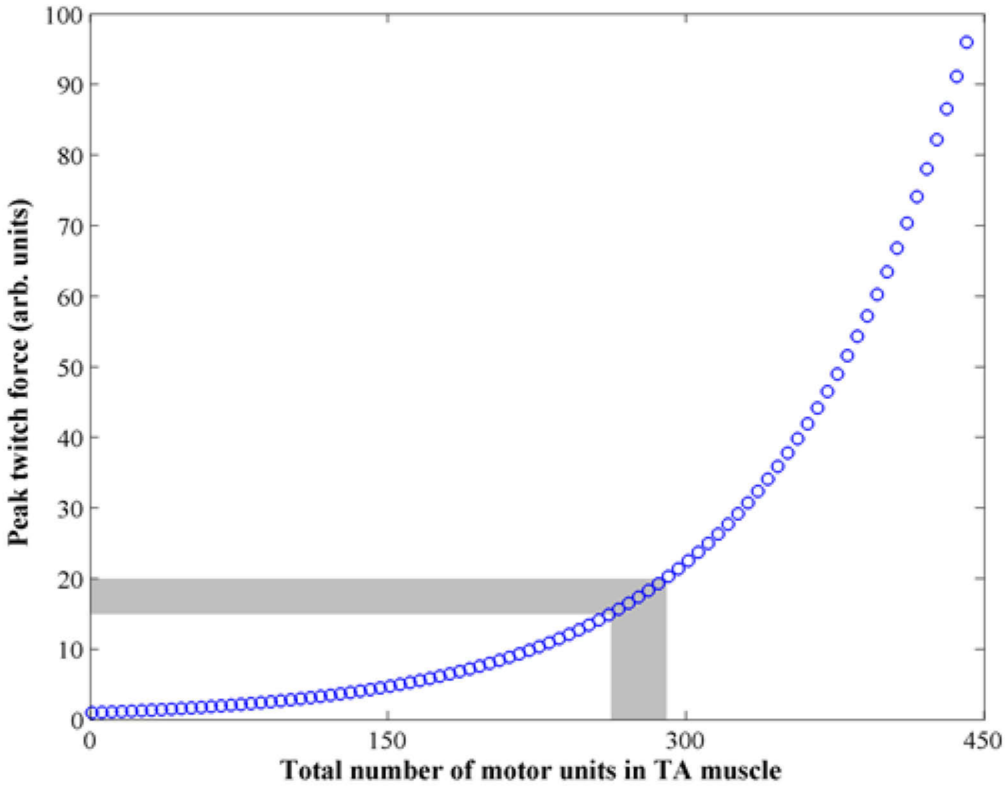

Figure 1-1: Motor unit recruitment and the size principle

The muscle motor unit pool recruitment is based on the size principle in ascending order of the muscle motor unit size. Fuglevand and coworker [54] proposed a simulation model to approximate the peak twitch force based on the total number of existing motor neurons and the range of twitch forces.

One important characteristic of MMUs is the rate of discharge of the recruited units. This discharge rate has been quantified using the Interspike interval, and is defined as the difference between two consecutive discharges (or action potentials) in time [45,54]. As in the case of any other part of the sensorimotor loop, intra-muscular conversion of synaptic input to generate action potentials or discharges, which are required for the generation of force, is also affected by noise. The presence of synaptic noise leads to variability in discharge patterns or interspike intervals even during steady synaptic excitations. The magnitude of the variability in interspike intervals has been measured using both SD as well as CV. In fact, earlier reports suggest that the CV of interspike intervals ranges between 0.1 – 0.3 for isometric contractions performed by human beings [50,54]. More importantly, it has been shown that fluctuations during force production tasks at a particular force level are related to the variability in the rate of the discharge of the recently recruited MMUs [22,60,78]. The quantification of variability in terms of fluctuations in force during voluntary contractions in various groups of muscles (finger abductors, knee extensors, ankle plantar- and dorsi-flexors) is therefore not only associated with intrinsic motor processes, but is also sensitive to the effects of system and task related perturbations.

1.1.4 Variability during whole-body static and dynamic task performance

During the performance of tasks such as static standing as well as walking, one of the essential constraints or conditions is maintaining balance. In order to effectively perform the activities of daily living the HSMS must ensure that the body's movement, inertial and supporting forces are is maintained in equilibrium. In physics, the term "*stability*" is considered to be the behavior of a system under small perturbations [79]. A stable system would therefore remain either in (or return to) a state of equilibrium under static conditions or in a state of uniform motion (maintain a specific trajectory) under dynamic conditions, after being perturbed [79,80]. During tasks such as standing or walking the position or location of the feet are negotiated by humans to manage the boundaries of the (projected) area of contact with the ground, termed the *base-of-support*, in order to maintain equilibrium. In order to maintain balance during upright static as well as dynamic activities, corrections to the base of support relative to the center of mass (located near the trunk) are provided by suitable foot placement, and in physical terms the behavior of the system is analogous to the *inverted pendulum*. For continuous motion, such foot placement, together with the body's trajectory therefore provide the primary mode of error correction to allow stable walking.

The assessment of variability observed during task related outcomes on a global or whole-body level has provided researchers additional insights into the behavior of the sensorimotor system. The variability observed over long durations has often been interpreted to represent the state of the system with respect to the stability boundary or base-of-support. During static tasks such as quiet standing, the human body is not only subject to gravitational forces [23,31,32,81,82,83,84], but also to changes in the internal as well as external conditions, all of which serve as challenges to the HSMS. In such situations, quantification of sway trajectories either in the presence or absence of perturbations can help to provide an understanding of the quality of the subject's postural control mechanisms.

Although during walking the human sensorimotor system is involved in a more complex process, the quantification of variability during task outcomes can be interpreted in a somewhat similar manner. During walking the HSMS is involved with simultaneous control of rhythmicity and coordination during the entire task cycle [16,40,43,68,85,86], balance mechanisms during stance and double support phases [40], while maintaining the required boundary constraints such as those needed for toe clearances etc. [87]. As in the case of static tasks, here too the human sensorimotor system acts primarily as a feedback control and the noise present in the motor system is one of the intrinsic sources of error in the outcome of the task. The quantification of variability during walking, i.e. variability of gait events, trunk motion, etc. both in the presence or absence of perturbations has helped researchers to not only better understand the effectiveness of the error corrections involved in the human sensorimotor system, but also has indirectly been used to represent the stability of the system.

If the fluctuations in force during isometric muscle force production tasks represent noise in the muscle motor output, it is likely that fluctuations during contractions of the lower extremity muscles e.g. knee extensions or ankle plantarflexions, will be related to variability during whole-body task performance such as standing and walking. It is therefore plausible that, assessment of fluctuations during isometric tasks could provide key information regarding the quality of the motor output, which might be used not only to identify and diagnose individuals with motor related pathologies.

1.1.5 Aging sensorimotor system

The quantification of stability and variability during task performance to quantify age- as well as fall-related motor deficits, has gained popularity in light of the increase in not only the proportion of geriatric but also fall-prone individuals across the world. Recent evidence suggests that larger levels of gait variability [13,40,43,64,68,88,89,90,91] and postural sway [18,65,66,67,84,92,93] are present in aged and, fall-prone, but also for those suffering from motor related pathologies, compared to their younger or healthier counterparts. The process of aging is generally associated with multiple phenomena such as apoptosis, oxidative stress, and elevated levels of cytokines [94,95,96]. While more description of exact mechanisms and detailed etiologies of such biological remodeling due to aging can be obtained elsewhere [94], one of the most important consequences of such phenomena is the loss in the amount of existing motor neurons [94,95,96]. Physiologically this leads to 1) loss in both the amount as well as the size of muscle fibers (also termed sarcopenia) and 2) the aging motor system undergoes a neuromuscular reorganization where the existing motor neurons tend to re-innervate other muscle fibers [75,94,97]. Such neuromuscular modifications have not only been shown to reduce the functional capacity, but have also been associated with an increase in variability while performing various tasks [22,40,91,98,99].

1.1.6 Effect of muscle fatigue on task performance

Fatigue is not only one of the most common results, but also remains to be universally perceived phenomena of repetitive or sustained task performance. Despite being such a universal phenomenon the definitions, physiological mechanisms and its effects of fatigue on task outcomes largely remain both controversial and ambiguous. Depending on the task and activity, fatigue can broadly be classified into mental workload [100,101,102] or physical fatigue [103,104,105,106]. Physical or whole-body fatigue is a widely accepted risk factor not only for work [104,107] or sports [108,109] related injury, but also for falling in elderly individuals [110]. As muscles are the only active component involved in producing force or effort, localized manifestation of fatigue in the muscles that are required to perform a task has challenged physiologists and movement scientists since the 19^{th} century [111]. Although, multiple definitions of muscle fatigue exist [112], it is characterized as the reduction in the ability of the muscle to produce a force upon sustained exercise [113].

Inducing muscle fatigue has been shown to increase fluctuation during force production [38,39,114,115,116,117]. The inability to generate a desired force output, largely leads to an increase in the required muscle activation to perform the same task in a non-fatigued state, and therefore recruitment of larger muscle motor units [22,73,112,117,118]. This increased muscle activation, at least at moderate force levels, can explain the increase in variability in force output [117,118]. Furthermore, inducing fatigue has also been shown to increase postural sway during standing as well as variability during walking [66,117,119,120].

Here, for both standing as well as walking, larger levels of variability experienced either post-fatigue or among aged individuals imply not only that the state of the system (or the center-of-mass located near the trunk) is likely to be closer to the stability boundary or at the limits of the base-of-support, but also that an increased level of corrective action is required by the respective HSMS in order to compensate for such a deviation from a stable center-of-mass position during task repetitions. In addition, introducing perturbations such as manipulating visual or somatosensory inputs [31,32,36] has similarly resulted in larger levels of variability. However, it remains unknown whether larger levels of variability during task performance are always an indicator of motor pathology [25,27,121].

It is currently unclear whether greater levels of variability is associated with motor related pathology [27,121,122,123]. In fact some studies have shown that optimum levels of variability during task performance is 1) essential for effectively learning and relearning a particular task [122,123] and 2) an important consequence of the presence of redundancy and adaptability in the motor system [124]. Furthermore, Brach and co-workers showed that the association between variability of step-width during walking and history of falling was, non-linear [121]. They showed that individuals with extreme levels of variability, both very high as well as very low, were more likely to have fallen in the past year compared to their counterparts that had moderate levels of step-width variability. It is likely therefore that, in addition to very high levels, lower than optimum levels of variability could also be an indicator of motor related pathology [121]. Thus, irrespective of the magnitude, different levels of variability during task performance do represent an inherent as well as a deterministic characteristic of the sensorimotor system rather than being a result of random error. Thus, assessment of variability during task performance as in the force fluctuations, postural sway and gait variability needs to be undertaken not only towards quantifying age- as well as fall-related functional deficits in a clinical setting, but also would provide better indices for predicting individuals with motor-related pathologies as well as designing rehabilitation programs.

1.1.7 Oscillatory patterns in task outcome during performance over longer durations

Although the magnitude of variability indeed represents a characteristic feature of motor noise, it fails to capture other important features that are important for assessing performances undertaken for longer durations. For example, another distinguishing feature of noise in the motor system is its oscillatory pattern or periodicity that is observed during most task performances undertaken continuously over longer durations of time. Most activities of daily living are generally undertaken for longer periods of time, for example, going for a walk, standing and waiting e.g. at a metro station, or gardening etc. all require repetitive performances of a basic set of tasks. During the performance of all of the aforementioned activities, multiple muscle groups need to be either activated repetitively or intermittently. In such cases, quantification of the magnitude of variability over the entire duration of the task fails to provide information regarding the sensorimotor system's ability to cope with perturbations such as fatigue or the ever-changing environment during task performance. Due to such limitations, quantification of only the magnitude of variability during task performance has not been able to find considerable success in clinical settings for identifying individuals that might possess motor related deficits [93].

The fluctuations observed during a force production task possess a unique oscillatory pattern. For example, let us consider a hypothetical case of a force production task with an individual requested to produce a target force of 50 N while pushing against a force pedal (dynamometer) with his/her foot for a period of 6 seconds (Figure 1-2). Let us also assume that in trying to do so the individual manages to produce the mean force of 51 N and an SD of 1.02 (CV = 0.02). Now, it is hardly difficult to consider a perfectly periodic signal such as a sine or a cosine wave to fluctuate around the force of 51 N and have an absolute noise of 1.02 N (Figure 1-2). Does this imply that the system and/or task characteristic represented a perfectly periodic signal? Although, the magnitude of fluctuations from both signals indicates such a possibility, it is highly unlikely. Due to such reasons, the magnitude of variability lacks the sensitivity as well as the predictive power towards describing the complexity of the task that was undertaken or for identifying force production deficits in the individual that had performed the task.

One traditional approach to characterize periodicity in the signal is to use Fast Fourier Transforms (FFT). This approach decomposes the fluctuation or variability in the signal into constituent frequencies. In other words, any[2] periodic signal that fluctuates around a mean can be decomposed in a histogram or a spectrum of frequencies. A simple sine wave (perfectly periodic signal), for example, will have only one frequency component, whereas a complex system might consist of a spectrum of frequencies. As shown in the previous example (Figure 1-2), different sine waves could be created with the same mean and SD of the inherent signal, but with different characteristic frequencies (Figure 1-2). In general, force produced from a human participant (Figure 1-2 E&F) possesses a band of frequencies ranging from 0 – 4 Hz [61,72,125] while the spectral content of postural sway during quiet standing possesses a range from 0 – 5 Hz [33,98,126].

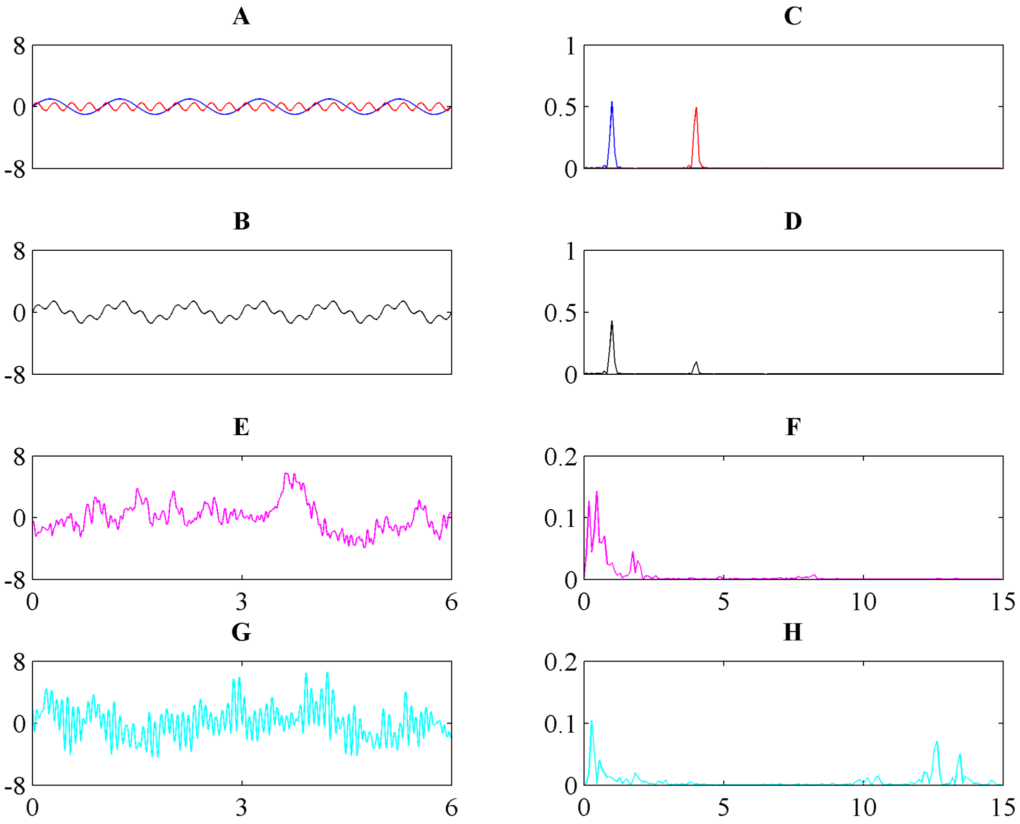

Figure 1-2: Analysis of signals in time- and frequency domain

Time- (A, C, E and G) as well as frequency-domain (B, D, F and H) illustrations of signals. A and B: Simple sine waves (A) with time periods of 1 (blue) and 0.25 (red), with corresponding frequencies (B) at 1 Hz (blue) and 4 Hz (red). C and D: A composite sine wave (C) comprising of the signals in A and the corresponding frequencies (D) again at the 1 and 4 Hz. E and F: Signal obtained during an isometric force production task performed at 15% of the maximum voluntary contraction from a young adult (E). The signal has been demeaned in order to scale it to 0. F: The frequency component of the signal in E. As compared to B and D the spectra here has a larger bandwidth implying that the force fluctuation signal consists of multiple frequencies ranging up to approximately 3 Hz. G and H: Signal obtained during an isometric force production task performed at 15% of the maximum voluntary contraction post-fatigue from the same adult in E. H: The frequency component of the signal in G.

One benefit of assessing spectral content of the signals (i.e. trajectories or forces) obtained during continuous task performance is that the larger the bandwidth of the resulting frequency or power spectrum, the more complex the respective task or system producing the signal is [127]. Furthermore, an analysis of the power spectra of a physiological time-series is able to not only provide a distribution of the inherent variance in the time-domain over a range of frequencies [48,71], but is also sensitive to complex attributes associated with physiological systems [128]. A direct benefit of such an approach is that it allows the performance of the system in the presence of external or internal perturbations to be quantified. For example, if the power spectrum from force fluctuations is assessed after inducing fatigue (Figure 1-2 H) an increase in power in the frequencies ranging from 8 – 12 Hz is observed. Thus, quantification of periodicity in the outcome of various tasks (e.g. standing or force production), when the human sensorimotor system is perturbed in the absence of sensory inputs, fatigue or aging, has provided important insights into not only the functioning of human sensorimotor system, but also its ability to compensate and acclimatize to various perturbations.

The quantification of spectral content of fluctuations during force production has allowed a deeper understanding of the mechanisms underlying the conversion of stimuli into a muscular force output. During force production, pairs of MMUs in from active muscles during maintained voluntary contractions in humans exhibit a tendency toward synchronized firing, which is thought to reflect the presence of a common presynaptic input to the motor neuron pool. This phenomenon is popularly known as MMU synchronization [50,57,59,62,129,130,131]. The processes responsible for MMU synchronization are transmitted within the muscle as a tension or length change and consequently may be observed as a tremor component in the signal [62,130,132]. One approach towards better understanding the MMU synchronization is to focus directly on the output signal. The argument stems from the belief that oscillations or periodicities in the motor cortex that modulate descending cortico-spinal pathways might result in a similar pattern of modulation not only of muscle electromyographic (EMG) activity, but also of movement in the form of a tremulous oscillation [130]. Although the etiology of the tremor components in the task outputs remain largely unknown, analysis of oscillatory patterns in the force outputs during isometric task, has indeed revealed some insights.

The firing rate for individual MMUs are mostly around 6 – 18 spikes/s [22,54,59,78,130,132][3]. During isometric force production, the *recently* recruited MMUs are synchronized producing a *fusion* of *twitch* contractions [22,54]. The phenomenon of fusion attenuates the firing rates of motor units, leading to a response that is very similar to convolution or superposition, between the input synaptic signal to the muscle and the output average force twitch from the MMUs [61]. This type of attenuation leads mostly to low-frequency components observed in the force output produced [61], previously demonstrated as 0 – 4 Hz components (Figure 1-2). In addition, it is also suggested that depending on other factors such as damping as well as stiffness in the musculoskeletal system, the time period of the cycle will either increase or decrease, thereby decreasing or increasing the frequency components of the patterns involved.

Fatigue is an intrinsic perturbation that is also known to affect the oscillatory pattern of the generated force. For example, performance of activities or contractions for longer duration of time reportedly lead to an increase in the firing rate of 6 – 10 spikes/s due to the onset of fatigue in the soleus muscles [132,133]. The spectral peaks in the region above 5 Hz in fluctuations during force production tasks are commonly known to represent the phenomena of tremor [61,131]. One of the most common forms of tremor is physiological tremor, which probably results from the rhythmic modulation of multiple motor units in turn caused by *stretch reflex oscillations* [134]. Although physiological tremor is known to occur commonly, it can severely impact task performance in situations such as under muscle fatigue, with aging or under pathologies [130,132,135,136]. Furthermore, the enhanced manifestation of such a pattern has been suggested to affect task performance during standing for longer periods of time [132]. Thus, the analysis of oscillatory patterns in the generated force is not only key towards understanding the functioning of the human motor system, but also provides information regarding the response of the system under perturbations as well as for elderly or individuals suffering from motor related pathologies.

Quantification of the spectral content of outcome measures from a task performed, repetitively has been undertaken in a similar fashion as in the case of force fluctuation signals. For example, during static standing, the analysis of spectral content of the postural sway signal has found success in detecting and discriminating postural control system (PCS) impairments [24,31,32,33,81,126,137], such as the spectral content of sway in subjects with ischemic blocking of leg afferents, by modifying visual or surface stimuli, fatigue, or with aging. Although, these reports suggest that spectral content of sway has been effective in identifying the PCS related discrepancies, measures of postural sway have still not found success in clinical setting for identifying individuals with motor related pathologies [24]. The reason for the lack of success of these measures is a need for understanding as well as better quantification of the effect of perturbations (internal as well as external) on the functioning of the PCS. In order to effectively accomplish these requirements the outcome measures (in this case postural sway outcomes) must be able to reflect not only the effect but also the extent of the effect depending on the type of perturbation. The use of power spectrum analysis on postural sway signals have been able to discriminate the contributions of the different afferent inputs to the PCS [24]. Analyses in the frequency domain therefore need to be undertaken in controlled experimental settings in order to elucidate both the periodic structure of task outcome signal as well as the changes in this structure depending on the type of perturbation. Quantification of the spectral content in such a fashion will help not only in identifying the complexity of the task output, but also in characterizing the behavior of the system under different internal as well as external conditions. Furthermore, such methods provide an approach to assess the ability of a subject to recover or deal with perturbations. Such analyses, in combination with the magnitude of variability, can therefore be used in the clinical settings in order to complement subjective clinical assessment, but also to not only effectively and prematurely diagnose individuals with motor related pathologies, but also aid towards designing targeted rehabilitation programs.

1.2 Purpose of the dissertation

The studies included in this dissertation target an improved understanding of the physiological and patho-physiological behavior of the human motor system by quantifying different aspects of variability observed during task performance. The presence of intra-subject variability during multiple repetitions of a task does not necessarily indicate motor related deficit or pathology. Instead, certain levels of force fluctuations and kinematic variability are known to be normal and indeed might be necessary for optimized task learning. Due to such controversies, a detailed understanding of variability during task performance still remains elusive. Furthermore, although stability during standing and walking are regulated via similar mechanisms within the human sensorimotor system, the variability during static (standing) and dynamic (e.g. walking) tasks have so far been viewed independently of each other. Finally, there is a lack of understanding in the literature in terms of the intrinsic or core system characteristics or mechanisms that might be responsible for variability during task outcomes. The approaches used to quantify both the magnitude and the oscillatory patterns of variability during various tasks as well as in the presence of different perturbations, could provide a clearer understanding of the functioning of the human sensorimotor system. Such approaches could then be used to complement current clinical practice for identifying individuals with motor-related deficits, but also designing targeted rehabilitation strategies.

Quantification of both the magnitude and the oscillatory patterns of variability during various tasks such as isometric force production, standing and walking, conducted in the presence or absence of either external (such as visual and surface conditions) and internal (such as fatigue and aging) perturbations, could help in understanding the state, as well as the behavior, of the human sensorimotor system. Furthermore, since fluctuations during isometric submaximal force production can indirectly be associated with neuromuscular noise, an understanding of the contribution of force fluctuations, on balance and walking performance would not only help to provide an understanding of the etiology of postural sway and gait variability, but might also aid in the early diagnosis of motor related pathologies, particularly in individuals with balance and gait deficits.

In order to achieve these overriding goals, we hypothesized that:

1) an increase in variability will be observed in the knee extensor force production tasks.

2) there is shift in the oscillatory pattern (power spectral profile) of force production task output signal towards higher frequencies post-fatigue.
3) higher levels of intra-subject variability during force production, posture and gait will be observed among individuals that have fallen in the 12 months prior to data-collection as opposed to their healthy age-matched counterparts.
4) there is a linear relationship between the variability during force production (neuromuscular noise) and variability during static as well as dynamic tasks.

In order to better understand the various aspects of intra-subject variability during task performance, the studies presented here in this dissertation therefore aimed to elucidate

1) The effect of fatigue as an intrinsic perturbation on intra-subject variability during isometric force production task.

2) The effect of intrinsic (age and gender) as well as extrinsic (visual or surface conditions) factors on intra-subject variability during static standing.

3) The role of force fluctuations (neuromuscular noise) in the lower extremity on postural sway and gait variability.

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1) There are exceptions to the generally accepted law of size principle. A common exception appears to be the recruitment pattern of motor units during eccentric contractions. For details please refer: [22,49,52,73,86,129]
2) The FFT holds true only for the assumption of stationarity and can only be performed for stationary signals. Signals that are stationary are assumed to have same values for mean and standard deviation for all periods. See [34,138,139,140] for details.
3) There is a lot of ambiguity surrounding the firing rates of different MMUs. For details please refer: [59,72,129,131,132,134,141,142,143,144,145].

2. Effect of fatigue on force fluctuations in knee extensors in young adults

This chapter has been adapted from:

Singh NB, Arampatzis A, Duda G, Heller MO, Taylor WR. 2010.
Effect of fatigue on force fluctuations in knee extensors in young adults.
Philos Transact A Math Phys Eng Sci, 368(1920): p. 2783-98.

For further details on the license agreements please refer to Appendices B and C.

2.1 Summary of the effects of muscle fatigue on force fluctuations

This study investigated the hypothesis that fatiguing exercises led to increased force fluctuations during submaximal isometric knee extensions and to decreased accuracy and steadiness in the time and frequency domains. Sixteen young adults (8 males, 8 females) were tested, in a seated posture with 90° knee flexion, to assess their ability to reproduce target extensor torques (TETs) set at 15% and 20% of their maximum voluntary isometric contraction, both before and after fatiguing exercises. Normalized mean (NMAE) and peak (NPAE) of the absolute error were both used to quantify accuracy, whereas normalized standard-deviation of the absolute error (NSAE) was used to quantify steadiness of the torque trials in the time domain. Mean and median power frequencies (MnPF, MdPF) and normalized peak power (NPkP) were used to assess the spectral structure of the torque signals.

NMAE, NSAE and NPAE all showed excellent intra- as well as inter-session reliabilities (ICC values > 0.75 and low SEM values), demonstrating repeatability of the test set-up. NMAE, NSAE and NPAE increased significantly post-fatigue (> 42%), together with a shift towards higher frequency (MnPF and MdPF) components, indicating that the set-up was sensitive enough to detect the decreased force accuracy and steadiness of the musculature after fatigue. Increased force variability in both the time and frequency domains could therefore explain decreased steadiness after fatigue.

2.2 Introduction to force fluctuations and muscle fatigue

Muscle weakness, particularly in the quadriceps and ankle dorsiflexors [146,147], has been identified as one of the major risk factors for falls [9,147,148]. Although muscle strength in the lower extremity has been correlated with gait parameters such as stride length and sit-stand performance, this primary parameter of muscle competence seems not to be related to improved endurance or static balance, or to restoring overall functional ability [149,150]. One plausible reason for this could be that most daily activities are performed at sub-maximal levels [41], thus rarely utilising the benefits that additional strength could bring. during voluntary sub-maximal contraction, force fluctuation is observed, caused by the recruitment of multiple motor units to exert the force, and which results in an inability of the musculature to generate constant forces [52]. Not only do such fluctuations hinder the capability to exert a desired force but they also impair the ability to produce an intended movement trajectory [47]. Consequently, the quality of the force produced can be assessed by quantifying both its accuracy, as the difference between a target force and the actual force generated, as well as the magnitude of the fluctuations, which can be considered a measure of steadiness [151].

Muscular force steadiness and strength both deteriorate with age [92,152], injury [153] and fatigue [58,92,99], which has also been associated with increased fall risk especially in older women [110]. This increase in unsteadiness has been reported in the upper extremity both during as well as after sustained contractions [114,154,155] and after repetitive fatiguing tasks [129,156]. However, except for a few studies on fatigue during sustained contractions [38,154], the relationship between fatigue and unsteadiness in the lower extremity, and therefore during functional activities, remains uninvestigated.

The inherent fluctuations during voluntary force production possess an oscillatory behavior that is comprised of a range of frequencies, normally between 0–3 Hz [55]. Physiological tremor, which results from the rhythmic modulation of multiple motor units caused by stretch reflex oscillations, however, has been reported to occur at frequencies of 8-12Hz [53,134,145]. Analyses in the frequency domain can therefore elucidate the periodic structure of this force variability, which is related to the underlying steadiness of the force production in the muscles and thereby effective task performance. The increased occurrence of tremor should therefore be visible as a shift towards higher frequency components of force generation after fatigue.

Since an increase in force magnitude has been associated with an increase in muscle activation [54,115,118,157] and a shift in spectral power towards higher frequency components [48], it is likely that the increased muscle activation associated with fatigue [54,115,157], even at the same loading levels, will result in a similar frequency shift. Moreover, increased muscle activation is thought to be responsible for additional variability (unsteadiness) in force production [39]. An understanding of the changes in force variability in both the time and frequency domains could therefore help explain the decreased steadiness as well as the increased fall risk in subjects that is associated with fatigue.

We therefore hypothesize that an increase in variability of the knee extensor force production will be observed post-fatigue, and that this increase in variability will be accompanied with a shift in power spectral profile of force signals towards high frequency components. The objectives of this study were therefore to firstly establish the reliability and reproducibility of force fluctuation measurements in the knee extensor test set-up and then quantify the effects of fatigue on force fluctuations in both the time and frequency domains.

2.3 Methods for testing the effects of muscle fatigue on force fluctuations

2.3.1 Participants

Sixteen young healthy adults (8 males and 8 females) from the local community, with no self-reported injuries, illnesses, or musculoskeletal disorders volunteered to participate in this study. Their mean (SD) age, body mass, and height were 28.9 (2.3) years, 71.8 (13.3) kg, and 176.8 (11.4) cm respectively. All participants provided written informed consent and the procedure was approved by the local Ethics Committee before beginning the experimental procedures.

2.3.2 Experimental Design and Procedures

Force fluctuations and accuracy of force control was assessed by measuring the ability of the knee extensors to steadily and accurately reproduce a target torque level in a standardized test set-up. In order to firstly assess the test-retest reliability of the experimental set-up, individuals were tested on three separate session days (min 48 hrs between sessions). To further investigate the effects of fatigue on force fluctuations, each participant was assessed one additional time on the final day, but directly after fatiguing squat exercises.

2.3.2.1 Test set-up

Individuals were seated on a dynamometer (Biodex 3 Pro, Biodex Medical Systems Inc., USA) in a standardized posture, using a belt to secure the pelvis (Figure 2-1). The rotational flexion/extension axis of the dynamometer was matched to the rotational axis of the knee joint, with the knee maintained at approximately 90° flexion. A cuff was tightened around the shank and the Biodex attachment to ensure that any relative movement was minimized. Since the measurements in this study were isometric and conducted at 90°, any errors due to inertia or gravity were avoided [158,159].

Prior to the start of each session, maximum voluntary isometric contractions (MVICs) of the knee were obtained, by providing standardized instructions and verbal encouragement to the participants to push as hard as they could, trying to reach their peak exertion 2-3 sec after the start of the trial. The MVICs, which lasted 5 sec, were measured three times with a minimum of 30 sec pause between contractions [152], with individuals provided with a further break after the stipulated pause, if needed. After ensuring that the highest recorded values were within 5% of each other, the maximum session value of all contractions was taken as the MVIC. Finally, 15% and 20% of this MVIC used as the reference target extensor torques (TETs) to assess torque control during testing.

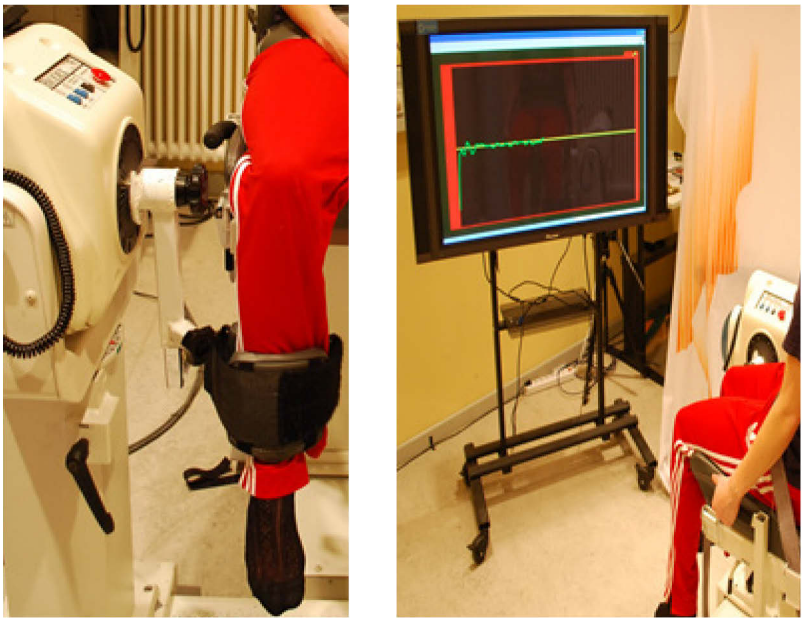

Figure 2-1: Experimental set-up for MVIC and muscular force fluctuation tests.

The dominant limb of the participant was first aligned with the rotational axis of the Biodex and then placed at 90° flexion and fastened to the Biodex attachment to avoid relative movement (left). Participants were requested to perform isometric knee extensions by pushing against the Biodex attachment. Target extensor torques (TETs) were displayed on a screen and participants were asked to match the target by performing knee extensions (right). Real-time visual feedback for the active torques was provided by overlaying the TETs on the screen.

2.3.2.2 Torque measurements

To assess the control of external torques, TETs, provided as constant torque plots (at 15% and 20% MVIC), were then displayed on the monitor and participants were instructed to match the torque level as well as they could for the duration of each test (approx. 15 sec) by performing isometric knee extension (Figure 2-1). The active torque applied by the participant was provided as a visual feedback at 10 Hz, which overlaid the TET. Participants were provided adequate practice sessions to familiarize themselves with the testing procedures. The presentation order of the signals was randomized with both TETs (i.e. 15% and 20% of the MVIC) presented 3 times.

2.3.2.3 Fatiguing exercises

After the pre-exercise torque control trials, each participant was requested to perform squat exercises, specifically chosen to induce fatigue in the knee extensors (quadriceps). An intermittent exercise protocol was used and participants were requested to start in an upright position with feet shoulder-width apart and with weights (approx. 40% body weight) carried on a barbell over the shoulders, squat down to approximately 90° knee flexion, and return to their start position. Each set of squat exercises consisted of 8 repetitions and a 30 sec rest-period was provided between sets. Each participant performed a minimum of 11 sets of squat exercises with the final set including continuous squats as long as participants could complete an entire repetition. The exercises were terminated when participants indicated that they were unable to perform the exercise further. To assess the extent of fatigue, a single post-exercise MVIC was measured, with at least a 15% reduction in the pre-fatigue MVIC observed in all subjects.

Post-exercise torque control trials were conducted immediately after the fatiguing exercises at the same level of torque as in the pre-exercise torque trials. The post-exercise measurements, for both the 15% as well as the 20% MVIC were conducted only once, in order to avoid the effects of recovery.

2.3.3 Data Collection and Analysis

2.3.3.1 Torque measurements

All torque measurements were collected at 3000 Hz, using Labview (Labview 8.6, National Instruments, Inc., USA). To avoid transients during initiation and termination of the torque trials, the first 7 and last 2 sec of data were removed (as in certain cases, participants required up to 5s to reach the target torques plus 2s boundary conditions). Each data set was then low pass filtered using 4^{th} order, zero-phase lag, Butterworth filter, with a 25 Hz cut-off frequency [50]. In addition, it was confirmed that little power (< 5%) of torque existed at frequencies > 25 Hz.

2.3.3.2 Time-domain measures

All measures evaluated in the study, were normalized to each participant's pre-fatigue MVIC. Accuracy of torque production was quantified using the normalized mean absolute error

(NMAE) of the torque signal, calculated as the average value of the absolute difference between the real-time participant exertion and the TET [153,160]. Force fluctuation (unsteadiness of torque production) was determined using the normalized standard-deviation of absolute error (NSAE), calculated as the standard-deviation of the absolute difference between the real-time participant exertion and the TET [39,152,153,160,161]. In addition, normalized peak absolute error (NPAE) was obtained to indicate the maximum deviation from the target signal.

2.3.3.3 Frequency-domain measures

In order to analyze the torque signals in the frequency domain, Fast Fourier Transform (FFT), after zero-padding, was used to calculate the power spectra for frequencies of the torque signal. Mean (MnPF) and median power frequency (MdPF) of the torque signals were then calculated as spectral measures of central tendency in the frequency-domain [93], to provide information regarding the distribution of power (amplitude) over the range of frequencies. Peak power in the spectrum was normalized to the total power in the torque signal spectrum (NPkP) at the modal frequency to provide a measure of the proportion of power that occurred at the dominant frequency [48]. To assess whether there was a shift towards higher frequency components in the torque signals post-fatigue, the power spectrum obtained from the FFT, was first normalized to the total power in the spectrum and then divided into low (< 4 Hz), middle (4 – 8 Hz) and high frequency (8 – 20 Hz) bands [48].

2.3.4 Statistical Analysis

2.3.4.1 Intra- and Inter-session reliability

The current study investigated the both intra- and inter-session reliability of torque control measurement set-up. For intra-session reliability assessment, 3 repetitions were taken into account from a single measurement session, and for the inter-session reliability, the average value of the 3 repetitions was taken for all dependent measures for each of the 3 separate sessions of measurement, pre-fatigue.

Intra-class correlations (ICC) were calculated to assess relative reliability of the torque control tests both within and between testing sessions [162]. Cronbach's alpha, as well as the standard error of measurement (SEM), were calculated as measures of the absolute reliability [163,164] of force fluctuation measurements between sessions, with sessions treated as a random effect [165]. ICC values are defined as the ratio between the true variance (difference between the total and error variances) and the total variance. The level of ICC therefore represents the level of consistency between the measurements as well as the agreement within measurements [166]. In this study the intra-session reliability was determined using the ICC(2,1) model to assess the individual repetitions within a session, and the inter-session reliability was calculated using the ICC(2,3) model to examine the mean of session repetitions [162]. Thus, for both intra- and inter-session ICC calculations a two-way random effects ANOVA was used, with both participants and sessions treated as random effects and the total error variance is split into inter-session variance and residual error variance [162,164]. ICC values range from 0 (no reliability) to 1 (perfect reliability), with ICC < 0.4 rated as poor, 0.4 to < 0.6 as fair, 0.6 to < 0.75 as good and ≥ 0.75 as excellent [166].

2.3.4.2 Effect of fatigue

A mixed factor ANOVA was conducted to analyze the effect of fatigue and force level on measures of force fluctuation. Both factors fatigue and force level had two levels each, fatigue (pre- and post-fatigue) and force level (15% and 20% MVIC). For pre-fatigue, the average value of the 3 repetitions from the session (day) was taken. Least significant differences (LSDs) were used to illustrate post-hoc comparisons. A significance level of $p < 0.05$ was set for all analyses. The SPSS software package (v17.0 SPSS Inc., USA) was used for statistical analyses.

2.4 Results of the effects of muscle fatigue on force fluctuations

In general, ICC, Cronbach's alpha and SEM indicated excellent levels of reliability for time domain measures for the test set-up at both (15% and 20% MVIC) pre-fatigue force fluctuation measurements for within as well as between test sessions (Table 2-1). Frequency domain measures displayed good to excellent reliabilities for within sessions, but lower values for between sessions. A significant decrease in steadiness and accuracy of torque control was observed post-fatigue.

Table 2-1: **Intra-session and inter-session reliability of force fluctuations**

The values for ICC, together with the 95%-ile one sided lower bound confidence interval (CIL), show the relative reliabilities. Cronbach's alpha (α) and standard error of measurement (SEM) are presented as measures of absolute reliability. The intra-session ICC was calculated using the ICC(2,1) model and the inter-session reliability was calculated using the ICC(2,3) model [162].

		Intra-session reliability				**Inter-session reliability**			
Force	**Measure**	**ICC**		**α**	**SEM**	**ICC**		**α**	**SEM**
		Mean	**95% CIL**			**Mean**	**95% CIL**		
15 [% MVIC]	**NMAE**	0.89	0.77	0.91	0.00	0.83	0.67	0.94	0.00
	NSAE	0.91	0.82	0.97	0.00	0.82	0.65	0.93	0.00
	NPAE	0.91	0.82	0.93	0.01	0.77	0.57	0.91	0.01
	MnPF	0.74	0.52	0.90	0.51	0.38	0.75	0.65	0.72
	MdPF	0.57	0.28	0.80	0.31	0.22	-0.07	0.46	0.69
	NPkP	0.75	0.54	0.90	0.03	0.38	0.08	0.64	0.04
20 [% MVIC]	**NMAE**	0.81	0.63	0.93	0.00	0.75	0.53	0.90	0.03
	NSAE	0.82	0.64	0.93	0.00	0.79	0.6	0.92	0.00
	NPAE	0.93	0.85	0.98	0.01	0.82	0.64	0.93	0.01
	MnPF	0.69	0.44	0.87	0.74	0.37	0.07	0.64	0.72
	MdPF	0.67	0.43	0.86	0.40	0.48	0.18	0.73	0.90
	NPkP	0.87	0.73	0.95	0.02	0.35	0.01	0.62	0.03

2.4.1 Intra- and inter-session reliability of force fluctuation measures

Intra-session reliabilities were excellent for time-domain measures NMAE (≥0.808), NSAE (≥0.817), and NPAE (≥0.914) during torque production (Table 2-1). Furthermore, low SEM values (≤0.006), for the same measures indicated high repeatability of the test set-up.

Inter-session reliabilities were also excellent (> 0.75) for all three measures (NMAE, NSAE & NPAE). Although not as low as the intra-session values, the inter-session SEM values still denoted high repeatability of the test-setup.

When the frequency domains of the torque signals were examined, intra-session repetitions resulted in ICC values of reliability that were good to excellent (0.567 – 0.868), but these were considerably lower for inter-session tests.

2.4.2 Effect of fatigue on force fluctuations

Fatigue led to a significant increase in all time domain force fluctuation measures (Table 2-2), with NMAE increasing by 47.7%, NSAE by 42.9% and NPAE by 52.1% post- fatigue (Figure 2-2). Significant main effects of fatigue were also observed in MdPF and NPkP with 71.7% increase MdPF and 20.1% decrease NPkP post-fatigue (Figure 2-3). Thus, not only did fatigue lead to reduced accuracy and steadiness in torque production tasks, but these fluctuations of torque also occurred at higher frequency components (Figure 2-3). In addition, the higher torque level (20% MVIC) led to significantly higher NMAE, NSAE and NPAE (Figure 2-2), demonstrating an increase in variability and inaccuracy in torque production at the higher torque level.

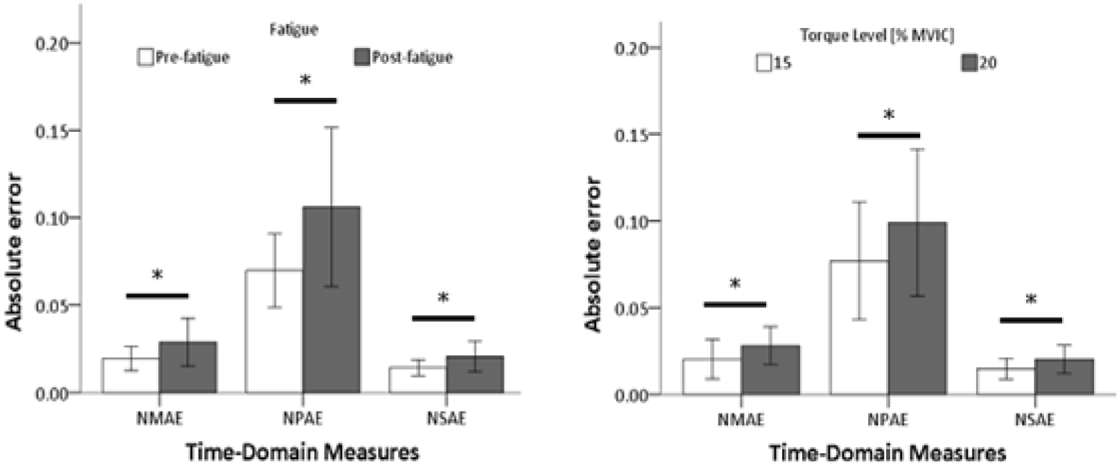

Figure 2-2: Effects of fatigue and the level of generated force on force fluctuations using time-domain measures

Effects of fatigue (pre- and post-fatigue, left) and level of generated force (15% and 20% MVIC, right) on time domain measures. The results show a decrease in both accuracy (Normalized mean (NMAE), normalized peak (NPAE) absolute error) as well as steadiness (normalized standard deviation of absolute error (NSAE)) during force production tasks post-fatigue and with increase in magnitude of the target force. * denotes $p < 0.05$.

Significant interactive effects of fatigue and force level were observed MnPF (Figure 2-3). Post-hoc comparisons showed higher MnPF post-fatigue compared to pre-fatigue, and 20% torque level led to a higher MnPF than the 15% torque level post-fatigue.

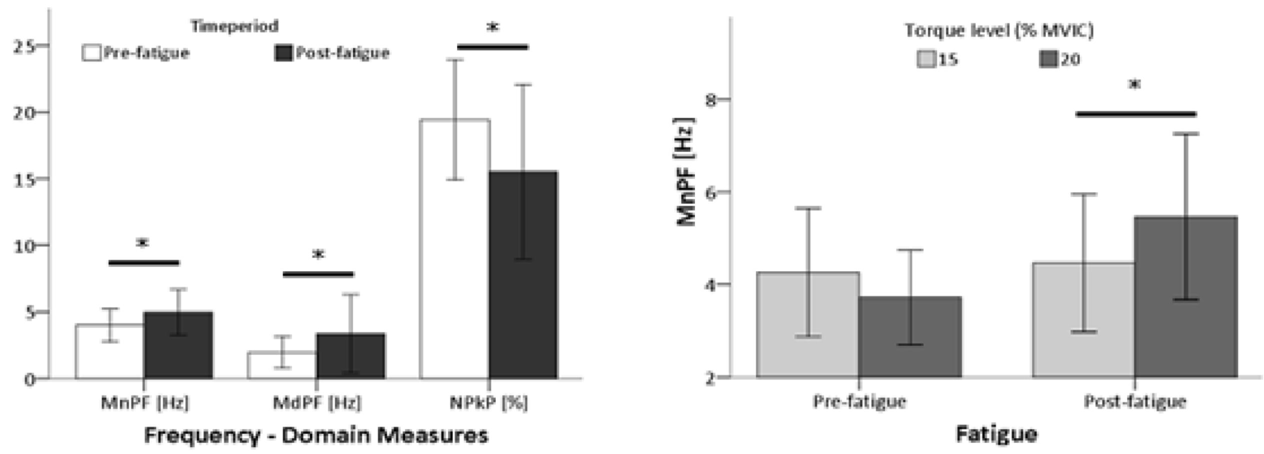

Figure 2-3: Effects of fatigue and force levels on frequency-domain measures of fluctuations

> The frequency-domain measures of mean (MnPF) and median power frequency (MdPF) and normalized peak power (NPkP) were used to analyze the effects of fatigue on force fluctuations. MnPF and MdPF are presented in Hz and normalized peak power (NPkP%) is presented as percentage of total power in the torque signal (left). Fatigue led to significant changes in MnPF, MdPF and NPkP ($p < 0.05$), indicated by *. Significant interactive effects of fatigue and force level were also observed on MnPF (right). Post-hoc comparisons revealed 20% MVIC led to higher MnPF as compared to 15% MVIC, indicated by *.

Fatigue led to a decrease in power in the lower frequency bands (< 4 Hz) accompanied by an increase in power in the higher frequency bands (8 – 20 Hz). There was no significant effect of fatigue in the middle frequencies (Figure 2-4), resulting in an overall shift towards higher frequency components in the torque signal after fatiguing exercises.

Table 2-2: **Effects of fatigue on force fluctuations**

Fatigue had a significant effect on force fluctuation measures in both the time- (NMAE, NSAE and NPAE) and frequency-domains (MnPF, MdPF and NPkP). Force level (15 or 20%) led to significant differences in NMAE, NSAE, NPAE and NPkP. Furthermore, MnPF had significant interactive effects of fatigue and force level. *p* values from ANOVA using fatigue, force level and the interaction between fatigue and force level are presented.

	Force fluctuation measures					
	NMAE	**NSAE**	**NPAE**	**MnPF**	**MdPF**	**NPkP**
Fatigue	< 0.001	< 0.001	< 0.001	0.001	0.003	0.001
Force level	< 0.001	< 0.001	< 0.001	0.389	0.294	0.026
Fatigue x Force level	0.65	0.180	0.086	0.006	0.096	0.410

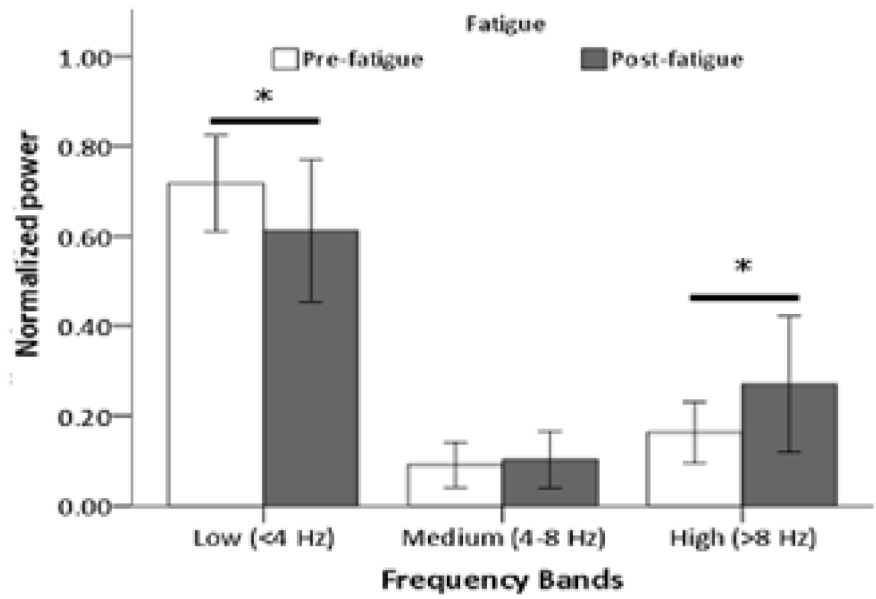

Figure 2-4: Effects of fatigue in different ranges of frequency bands

A significant decrease ($p < 0.05$) in normalized power in the lower frequency band (< 4 Hz) was accompanied by a significant increase in power in the higher frequency bands (> 8 Hz), indicating physiological tremor. The symbol * indicates significant differences between pre- and post-fatigue proportional power in the low and high frequency bands respectively. There were no differences in the middle frequencies after fatigue.

2.5 Discussion of the effects fatigue and levels of generated force on the fluctuations in the output

An understanding of the changes in force variability in both the time and frequency domains could help explain the decreased steadiness and the fall risk in subjects that is associated with fatigue [110]. Since the relationship between fatigue and unsteadiness in both the time and frequency domains of the lower extremity remains uninvestigated, this study aimed to determine whether a reduction in steadiness of the force signal is associated with a shift towards higher frequency components. As a first step, the reliability and repeatability of a torque control test set-up was established by assessing young, healthy subjects and used to test the change in levels of force fluctuation after fatiguing exercises. The results indicated that time-domain measures of accuracy and steadiness of continuous torque production had excellent reliabilities [162,166], whereas frequency-domain measures had relatively lower values of reliability. Furthermore, fatiguing exercises led to reduced accuracy and steadiness in continuous torque production of the knee extensors and the associated torque signal showed a shift towards higher frequencies.

Using the set-up in the current study, accuracy of the torque production (NMAE) was found to be approximately 1.5 – 2.3% of the MVIC at 15% and 20% torque levels respectively (Figure 2-2). These results are completely in agreement with Hortobágyi and co-workers [153], who reported a force accuracy for the control of quadriceps muscle force within 2-3% of the target force. The slightly lower values observed in our study could be due to the fact that subjects' force production was normalized to the maximum isometric contractions. Similarly the values for the standard deviation of the absolute error (NSAE) normalized to the MVIC, ranged from 1.2 – 1.6% of the MVIC. These values are analogous with the normalized standard deviation of force reported as approximately 2% of the MVC for continuous force production [118,152].

Although the reliability of frequency-domain measures for postural sway, particularly mean and median power frequencies, are known to be lower than time-domain measures [63,167], the reliability of quantifying force fluctuation measures, in either the time or frequency domains, has remained uninvestigated. Both the intra- and inter-session reliabilities of the test measures in 16 subjects in this study were found to be excellent in the time-domain. Measures in the frequency-domain, on the other hand, showed intra-session reliabilities ranging from good to excellent, whereas the inter-session reliabilities were only poor to fair (Table 2-1). Furthermore, force fluctuation measures were more reliable at 15% MVIC force production task than at the 20% MVIC task. Since, all participants were measured on the same standardized experimental set-up any lower levels of inter-session reliability were more likely to be due to the natural variability associated with the phenomena of force fluctuation than any differences associated with e.g. seating posture. Frequency domain measures provide an insight into the periodic structure of the force fluctuations [71]. Low inter-session reliability in the frequency-domain relative to the time-domain would therefore suggest that although the accuracy and steadiness levels of the generated force are repeatable between sessions, the periodic structure of the generated force is more variable. This variability seems to be associated with the physiological organization of the motor unit pool [118], including recruitment of the motor units [58,60,141] and synchronization of the motor unit pool [134]. From the results of this study, it seems that during submaximal voluntary contraction, motor units are recruited in a pattern that ensures effective task performance (as demonstrated by measures of accuracy and steadiness in the time-domain), but that the periodic structure of the generated force is affected by an inherent shakiness, or physiological tremor [53,134,145]. Assessment in the frequency domain therefore appears to allow access to an understanding of shakiness or tremor in the generated force.

ICCs have been used in this study to assess the reliability of the test set-up. While this method has been criticized as a predictor of reliability, it provides a value of consistency as well as agreement between measurements. If the variance between subjects is high, even though the intra-subject variance may be low, it is still possible to obtain high values of ICC. In order to resolve these issues, SEM and Cronbach's alpha, as measures of absolute reliability, have also been presented. SEM values were lower for time-domain measures, indicating good average reliability. Intra-session Cronbach's alpha values were generally higher for 15% MVIC levels as compared to the 20% MVIC levels, suggesting that fluctuations at higher force production levels might be less repeatable.

Force fluctuations during voluntary contractions occur due to the fact that multiple motor units are recruited by the muscle at submaximum levels, with increasing force levels resulting in increased fluctuations [48,151]. This increase in fluctuation is reportedly a result of the increase in the number of motor units recruited and is thus constrained by the total number of units in the muscle. Here, decreased accuracy was shown by higher NMAE and NPAE, and decreased steadiness shown by increased NSAE (Figure 2-2) in force fluctuations with increased levels of force matching tasks; at 15% as compared to at 20% MVICs. These results are in agreement with the previous studies that reported that higher levels of submaximal force output resulted in greater inaccuracy and unsteadiness, in particular at lower levels of effort [48,151,168].

The post-fatigue shift in spectral components of the torque signal towards higher frequencies (increase in mean power frequency), in combination with the reduction in proportional peak power, provides evidence of the broadening of spectral power structure. This implies increased noise in the signal as well as greater periodicity in the force variability measurements [48]. Furthermore, Missenard and co-workers [118] showed that increased muscle activation during fatigue was the factor responsible for increased force variability, suggesting physiological organization of the motor unit pool as a possible reason. The results of this study showed decreased normalized power in the low frequency band, no differences in the middle frequencies, but increased normalized power in the high frequency band, post-fatigue. Here, it is likely that either more motor units are recruited to perform the same task or that the firing frequencies of the same recruited motor units are enhanced [37,39,141,157,169]. The resulting shift towards higher frequency components of the generated force post-fatigue, particularly at frequencies between 8 - 12 Hz, is consistent with the occurrence of physiological tremor [53,55,134,145]. The results presented in this study indicate that fatigue perturbs the production of force, with the output fluctuating not only at a higher magnitude but also at a higher frequency, resulting in increased force signal complexity or noisiness (periodicity in the force signal), such as increased tremor in the force signal. The shift towards higher frequency components observed in this study after fatiguing exercises seems therefore to be indicative of higher levels of muscle activation as well as an increase in physiological tremor, and therefore confirms the study hypothesis.

The results of this study have demonstrated that reduced levels of accuracy and steadiness of force production and a broadening in the power spectral profile occurred post-fatigue. This is important for the quality of task performance during activities of daily living [47]. These results confirm not only that fatigue led to an increase in the magnitude of variability of the force production, but also resulted in a change in the structure of the force production signals, indicative of decreased steadiness [48] and increased tremor [55]. Such changes in the quality of task performance after fatigue may contribute to the additional fall risk in the elderly [110]. Although a shift towards higher frequency components in the force signal after fatigue has been shown in young healthy subjects, it seems that this broadening of the spectral components, together with the associated unsteadiness of force control, could play a role in understanding control mechanisms during fatigue.

3. The spectral content of postural sway during quiet stance: influences of age, vision and somatosensory inputs

This chapter has been adapted from:

Singh NB, Taylor WR, Madigan ML, Nussbaum MA. 2011.
The spectral content of postural sway during quiet stance: influences of age, vision and somatosensory inputs.
J Electromyogr Kinesiol. 22(1): 131-6.

Please refer Appendix C for details on the license agreement.

3.1 Summary of spectral content of sway

Maintenance of human upright stance requires the acquisition and integration of sensory inputs. Conventional measures of sway have had success in identifying age- and some disease-related changes, but remain unable to address the complexities and dynamics associated with postural control. We investigated the effects of vision, surface compliance, age, and gender on the spectral content of center of pressure (COP) time series. Sixteen healthy young (age 18 – 24) and older participants (age 55 – 65) performed trials of quiet, upright stance under different vision (eyes open vs. closed) and surface (hard vs. compliant) conditions. Spectral analyses were conducted to describe COP mean normalized power in discretized bands. Effects of the two sensory modalities and age were distinct in the antero-posterior and medio-lateral two directions, and a reorganization of spectral content was evident with increasing task difficulty (eyes open vs. closed and hard vs. compliant surface) and among older adults. These results indicate that vision and surface compliance are predominantly associated with responses from musculature associated with antero-posterior and medio-lateral directions of sway, respectively. Finally, distinguishing between the contributions of different afferent systems to the postural control system using the spectral content of sway bi-directionally may help in diagnosing individuals with balance impairments.

3.2 Introduction to the spectral content of sway

Quiet standing, although a seemingly trivial task, is inherently unstable. Gravitational forces, imparted on what can be considered an unstable inverted pendulum [24,81,82,83,84,170,171], along with alterations either external (e.g. perturbations or quality of visual input) or internal (e.g. fatigue, aging) to an individual, all serve as challenges to the postural control system (PCS). The PCS acts primarily as a feedback control system [24,81,82,170,171], acquiring and integrating diverse afferent inputs and generating adaptive and corrective motor commands.

Assessments of PCS function have often been based upon data obtained during trials of quiet, upright stance. A variety of measures have been derived, based typically on either center-of-mass [126,172,173] or center-of-pressure (COP) [65,172,173,174] time series. Although spatio-temporal measures and measures based on frequency-domain analyses have been reasonably successful in identifying age- and disease-related differences, questions remain as to their value as potential biomarkers for impaired balance [93]. Analysis of the power spectra of physiological time-series is able to not only provide a distribution of the inherent variance in the time-domain over a range of frequencies [175], but is also sensitive to complex attributes associated with physiological systems [127]. More specifically, analysis of spectral content has found success in detecting and discriminating PCS impairments [24,33,81,126,137,170,171], such as the spectral content of sway in subjects with ischemic blocking of leg afferents [176].

Our focus here is on whether and to what extent the spectral content of COP reflects, or can be used to indicate, PCS functioning related to selected aspects of the internal and external environment. Recent evidence suggests that the use of power spectrum analyses on COP time series can discriminate the key contributions of vestibular, visual, and somatosensory inputs to the PCS at different frequencies [33,98,126,177,178]. Specific frequencies that reflect each sensory modality, however, are still the subject of discussion [33,98,126,178], and ambiguity exists in terms of the range of total frequency content [33,98] and bandwidth size [33,98,126,178]. Thus, there are a lack of definitive recommendations in terms of the frequencies at which these postural responses occur, or to which each sensory system contributes, an issue that is key to understanding not only the effectiveness of the PCS at integrating diverse afferent inputs but also the quality of motor commands.

While the influence of visual input and age on the spectral content of postural sway has been previously demonstrated [93,137], potential interactive effects of sensory modalities with age or gender on the spectral distribution of the postural sway have not been reported. Furthermore, the PCS appears to use distinct control strategies in the anteroposterior [126] and mediolateral (ML) directions [170], and these strategies may be differentially altered with age [93,98,137,179]. Finally, information regarding the distribution of variability at different frequencies would not only help in distinguishing between the effects of various sensory modalities on sway but also in designing patient-specific rehabilitation programs that are aimed at improving balance. We thus investigated the effects of visual and somatosensory inputs on the frequency distribution of sway bi-directionally and with respect to differing age and gender.

3.3 Methods for testing the effects of visual and somatosensory conditions on the postural content of sway

Data were obtained from a prior study [180], involving 16 young (aged 18 – 24) and 16 older participants (aged 55 – 65), gender balanced in each group, recruited from the local community. No participant had any self-reported injuries, illnesses, musculoskeletal disorders, or occurrences of falls in the previous year. Each participant completed an informed consent procedure approved by the local Institutional Review Board.

Following initial practice and familiarization, participants completed several trials (75 sec each) of quiet, upright, bilateral stance in four conditions, involving manipulations of visual (eyes open and closed) and somatosensory feedback (compliant and hard standing surface). Individuals were requested to stand as still as possible, with arms by their side. In the eyes open condition, participants focused on a small cross, placed at eye level and 75 cm in front of them. In the compliant surface condition, a foam board (thickness = 2.3 cm) was placed on a force platform (AMTI OR6-7-1000, Watertown, Massachusetts, USA). Three replications of each condition were completed in a randomized order, with at least one minute between each trial.

During trials, participants stood on the force platform, from which triaxial ground reaction forces were sampled at 100 Hz. These were subsequently transformed to obtain COP times series [181] in the AP and ML directions, with the initial 10 and final 5 seconds deleted to remove boundary effects. To assess stationarity of the current COP time series, the COP signals were first low-pass filtered (Butterworth, 2nd order, bi-directional, 15 Hz cut-off frequency), and then a subset of the data was analyzed using both the Kolmogorov-Smirnov distance (Cao et al. 2004) and the exponent from detrended fluctuation analysis (Peng et al. 1995). After zero padding to 8192 data points and de-meaning, Fast Fourier Transforms (FFTs) were used to obtain power spectra up to 10 Hz for each COP time series. Each power spectrum was then normalized to the total signal power and divided into 100 bands with width = 0.1 Hz. Finally, the mean normalized power (MNP) was calculated for each band across the three repetitions within each vision and surface condition.

Mixed-factors analyses of variance (ANOVAs) were used to assess the effects of vision (eyes open vs. closed) and somatosensory feedback (compliant vs. hard surface), both as within-subjects factors, as well as age and gender (included as between-subjects, or blocking, factors). MNPs within each band were the dependent variables, with separate ANOVAs performed for each spectral band and direction. Prior to these analyses, MNP values were natural-log transformed (which yielded normally distributed, homogeneous residuals). Since a total of 100 ANOVAs were performed in each direction, adjustments for multiple post-hoc pairwise comparisons were made by controlling false discovery rates (FDR) with a threshold rate of 0.05 (Benjamini and Hochberg, 1995). Generalized eta-squared (η2) was calculated as an effect size (Olejnik and Algina, 2003) to estimate the proportion of variance in each spectral band due to sensory conditions, age, and gender. All statistical analyses were conducted using SPSS Statistics 18 (IBM SPSS Statistics, USA). Results are given based on the center frequencies of each band (i.e., 0.05, 0.10, 0.15, … , 9.95 Hz).

3.4 Results of changes in the visual and somatosensory conditions on postural sway

Results from both the Kolmogorov-Smirnov distance and exponents from detrended fluctuation analysis provided no evidence of deviations from stationarity. Main effects of surface (Figure 3-1) and vision (Figure 3-2) on MNP_{AP} were evident for specific frequencies. Significant main effects of surface compliance were observed at eight frequency bands (centered at 0.05, 0.25, 0.35, and 3.25 – 3.65 Hz), while effects of vision on MNP_{AP} were significant in almost all bands < 9 Hz. In the lowest band (0.05 Hz) increased spectral content was observed for hard surface and eyes open conditions, whereas in all other higher frequency bands increased power was observed with the compliant surface and eyes closed conditions.

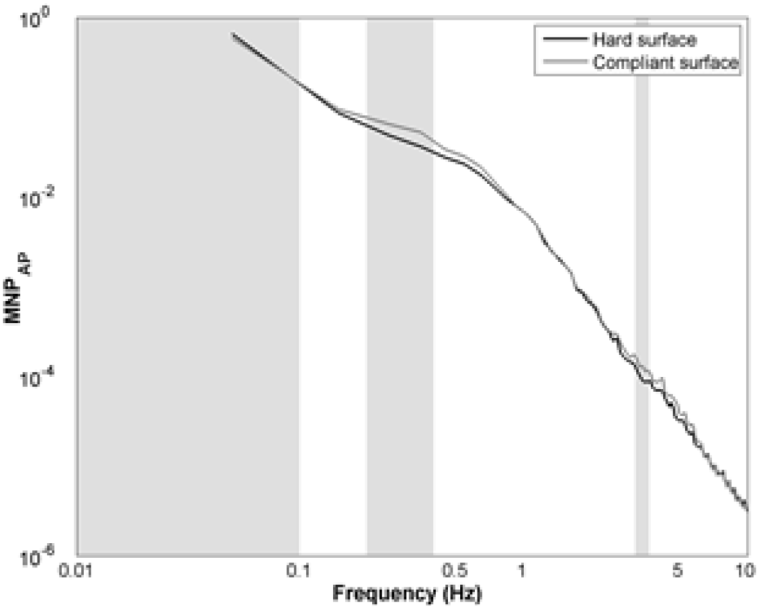

Figure 3-1: Effects of surface conditions on spectral content of sway

Effects of surface conditions on mean normalized power (MNP) as a function of frequency in the anteroposterior (AP) direction. Data are presented on log-log axes (base 10). Mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz), and grey areas indicate specific frequency ranges for which there were significant surface or vision effects.

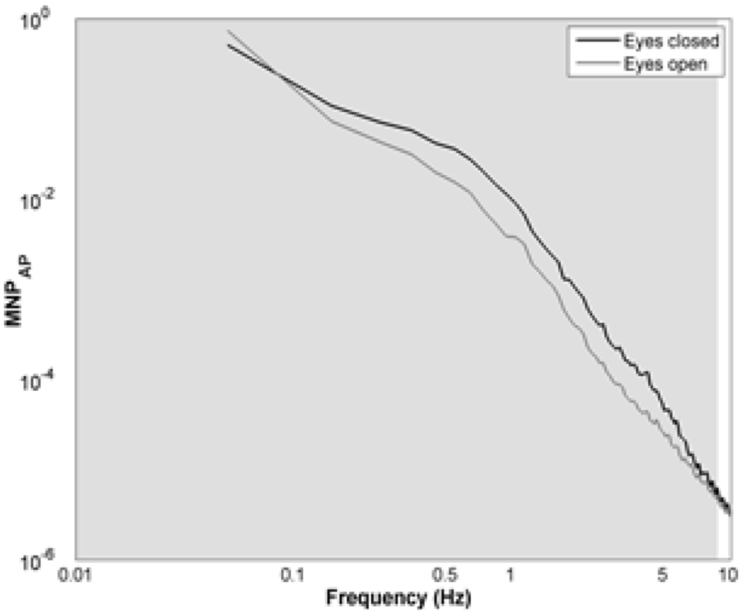

Figure 3-2: Effects of visual condition on the spectral content of postural sway.

Effects of visual condition on mean normalized power (MNP) as a function of frequency in the anteroposterior (AP) direction. Data are presented on log-log axes (base 10). Mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz), and grey areas indicate specific frequency ranges for which there were significant surface or vision effects.

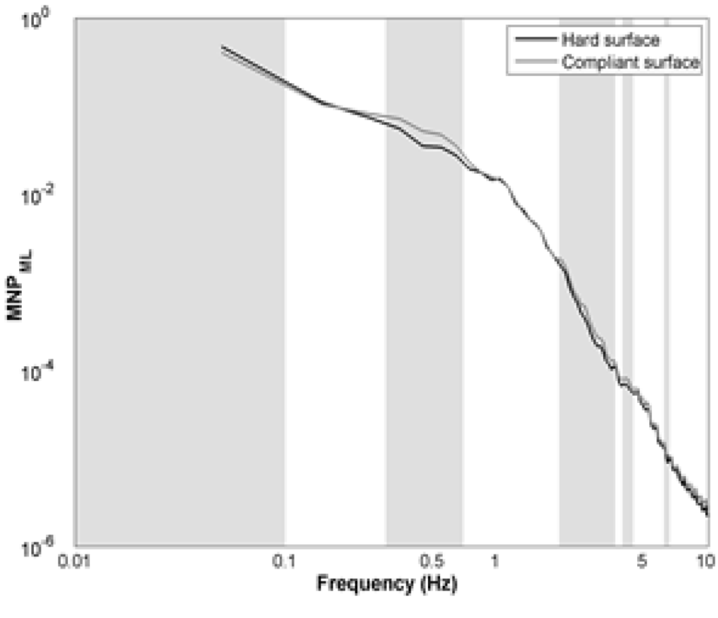

Figure 3-3: Effects of surface conditions on the spectral content of sway

Mean normalized power (MNP) as a function of frequency in the mediolateral (ML) direction. Data are presented on log-log axes (base 10). Mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz), and grey areas indicate specific frequency ranges for which there were significant surface or vision effects.

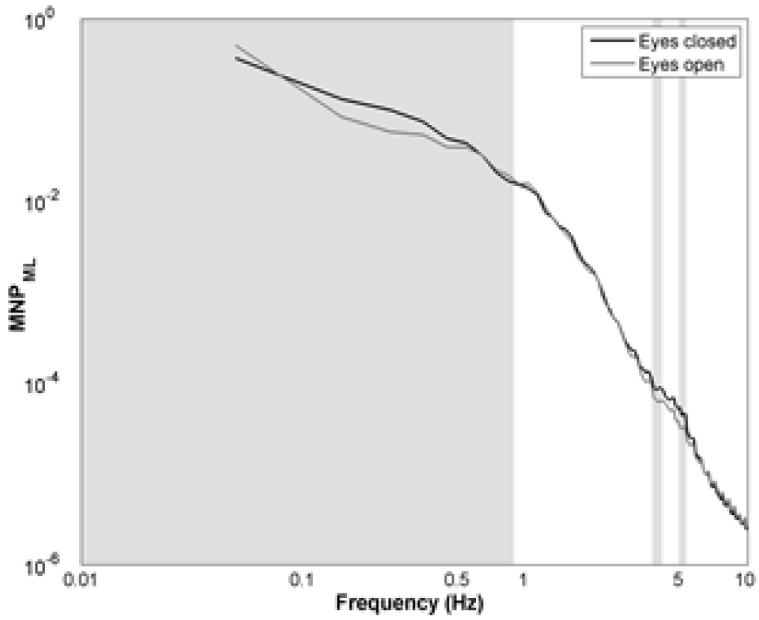

Figure 3-4: Effects of visual conditions on spectral content of sway

Mean normalized power (MNP) as a function of frequency in the mediolateral (ML) direction. Data are presented on log-log axes (base 10). Mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz), and grey areas indicate specific frequency ranges for which there were significant surface or vision effects.

Significant main effects of surface (Figure 3-3) and vision (Figure 3-4) were also observed on MNP_{ML}. Surface compliance had significant effects in several bands across the spectrum, including those at very low (0.05 Hz), low to middle (0.35 – 0.65 Hz), middle to high (2.05 – 3.65 Hz) and high (4.05 – 4.45 and 6.25 – 6.65 Hz) frequencies. Significant main effects of vision were observed in low and low to middle frequency bands (0.05 – 0.85 Hz) as well as in several high frequency bands (3.85 - 5.35 Hz). Similar to the AP direction, there was increased power for hard surface and eyes open conditions in the lowest band (0.05 Hz), whereas at higher frequency bands more power was observed in the eyes closed and compliant surface conditions.

There were also main effects of age on MNP_{AP} (Figure 3-5) in two frequency bands centered on 0.75 and 0.85 Hz, although older individuals had higher values in most bands except at the lowest frequency and high frequencies. Older individuals had higher MNP_{ML} in most bands except the lowest (Figure 3-6), especially in frequency bands between 0.85 and 1.95 Hz and in high frequency bands (4.35 – 5.45 Hz).

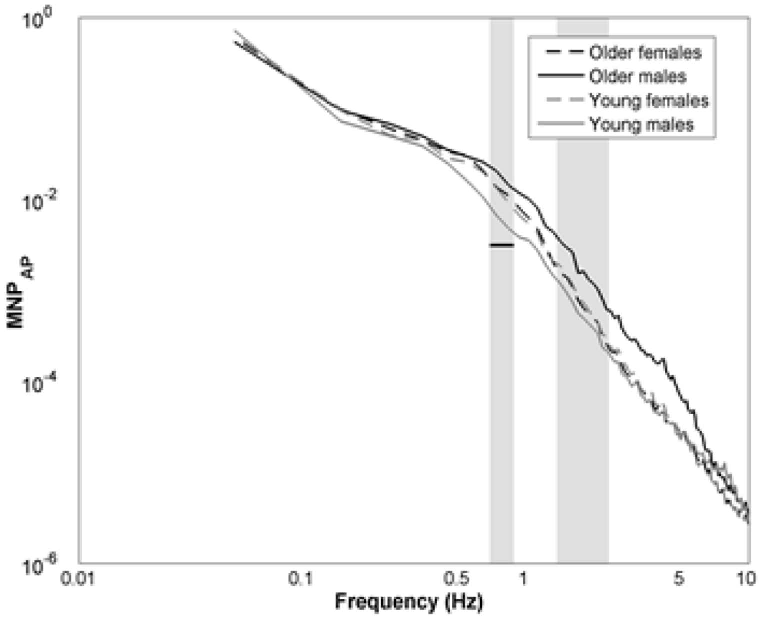

Figure 3-5: Age and gender differences on the spectral content of sway

Mean normalized power (MNP) as a function of frequency in the anteroposterior (AP) directios. Data are presented on log-log axes (base 10). Mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz). Horizontal black bars indicate significant main effects of age, and grey areas indicate specific frequency ranges for which there were significant age x gender interaction effects.

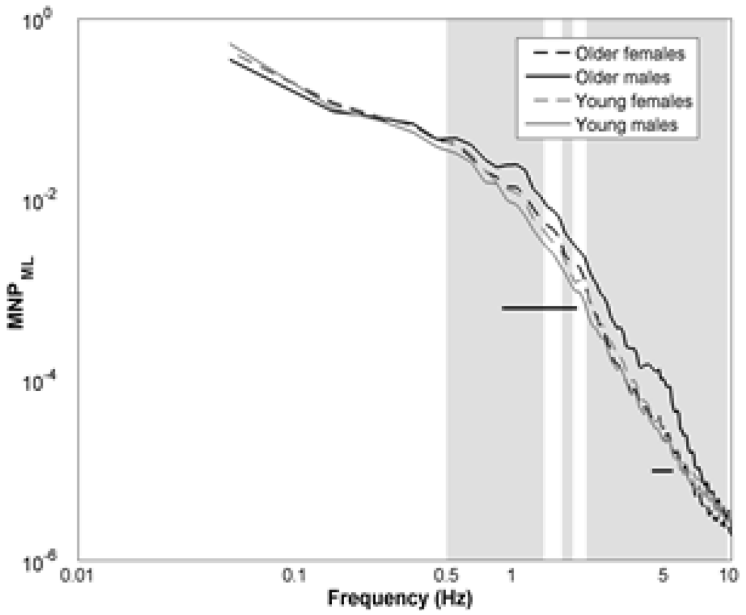

Figure 3-6: Age and gender differences on the spectral content of sway

Mean normalized power (MNP) as a function of frequency in the anteroposterior (AP; a) and mediolateral (ML; b) directions. Data are presented on log-log axes (base 10). Mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz). Horizontal black bars indicate significant main effects of age, and grey areas indicate specific frequency ranges for which there were significant age x gender interaction effects.

Interactive effects of age x gender were present on MNP_{AP} (Figure 3-5) and MNP_{ML} (Figure 3-6), though these effects occurred at different frequency bands. These effects were significant in middle frequency bands for MNP_{AP} (0.75 – 0.85 and 1.45 – 2.35 Hz) vs. middle to very high frequency bands for MNP_{ML} (several bands ranging between 0.65 and 9.75 Hz). At the significant frequency bands, the increase in both MNP_{AP} and MNP_{ML} among older individuals was generally more pronounced in males than in females. In addition, older males showed higher levels of MNP than the remaining three groups at the highest frequency bands in both the AP and ML directions. Older males also exhibited distinct behaviors in the lowest frequency band (0.05 Hz), having the lowest levels of any age/gender group, a pattern that was consistent in both directions (AP and ML). Figure 3-7 provides an overall summary of the significant effects on MNP at various frequencies, clearly suggesting that vision had a more distributed effect in the AP direction as compared to ML, with effects in ML mostly evident at frequencies below 1 Hz. In contrast, effects of surface were apparent at middle ranges of frequencies in both directions, in addition to some high frequencies in the ML direction.

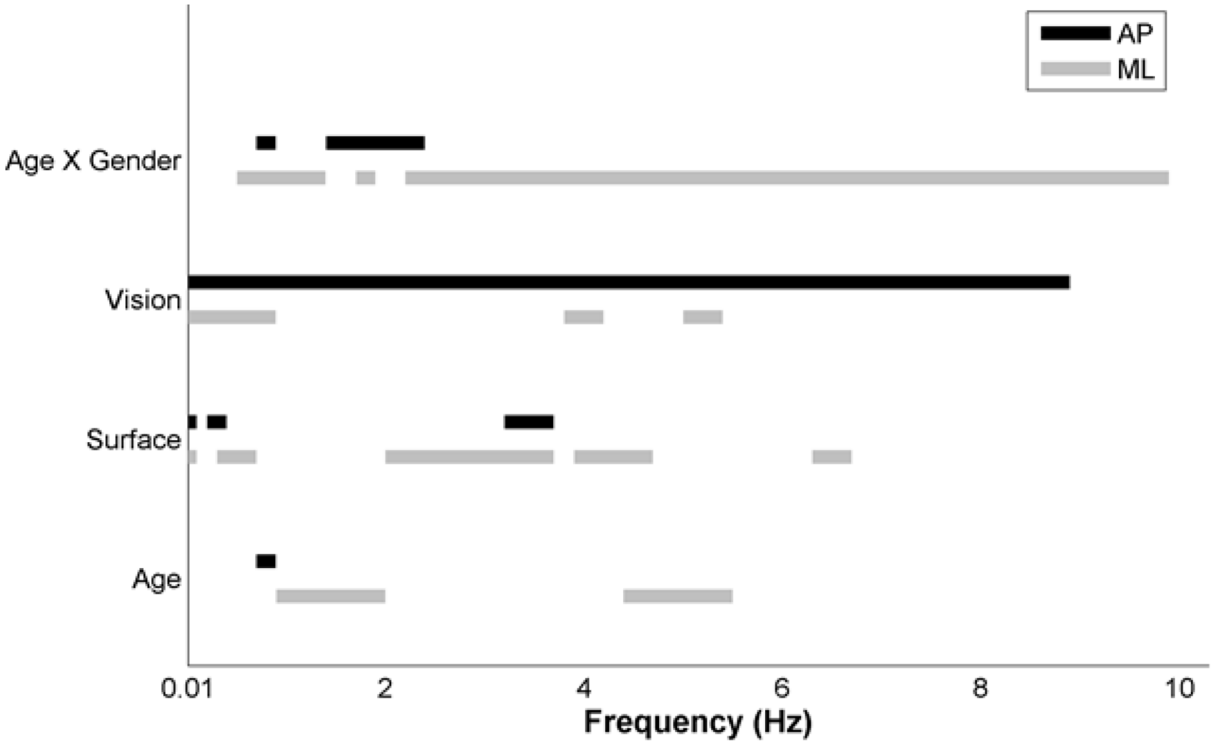

Figure 3-7: Summary of significant age, surface, vision, and age x gender effects on the spectral content of sway

Mean normalized power (MNP) in the anteroposterior (AP; black solid lines) and mediolateral (ML; gray solid lines) directions. Lines indicate ranges of frequencies at which a given effect was significant on the respective MNP values. Note that frequency is presented on a linear scale.

In the AP direction, effect sizes (η^2) for age, age x gender, surface, and vision on MNP were less consistent for lower frequency bands (i.e. <1 Hz) in terms of magnitude and the relative influences of each factor. However, at frequency bands between roughly 1 and 5 Hz (Figure 3-8) effect sizes were largest for vision and smallest for surface condition, whereas frequency bands above 6 Hz gender had the largest effect sizes (Figure 3-10). A more complex pattern was evident in the ML direction. At the lowest frequency bands (i.e. <1 Hz), effect sizes for vision were the most substantial (Figure 3-9), whereas for frequency bands between about 1 and 5 Hz effect sizes for surface and vision conditions were quite small. Here, the effects of age and age x gender were dominant, whereas at high frequency bands (8 – 10 Hz) the effect sizes of surface and age x gender were large (Figure 3-11), with their relative influence varying with frequency.

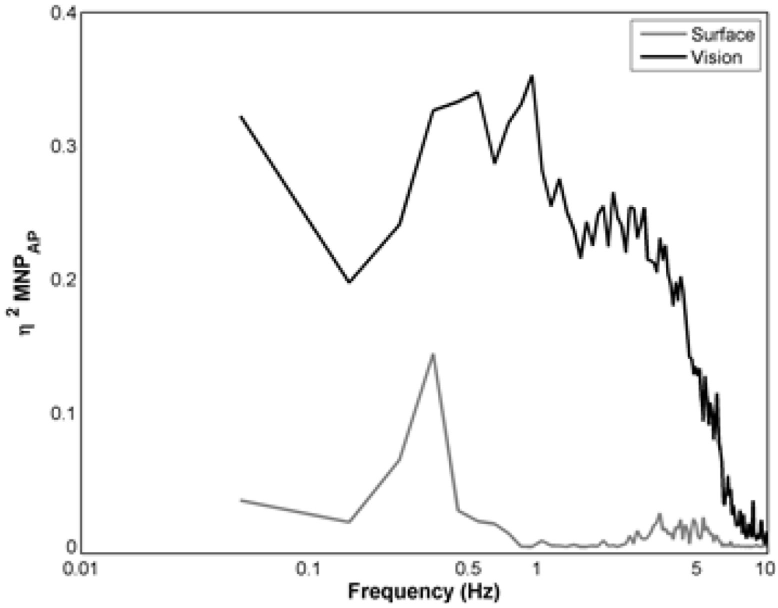

Figure 3-8: Effect sizes (η^2) corresponding to the influences of surface, and vision on the spectral content of sway

Mean normalized power (MNP) in the anteroposterior (AP; a and c) and mediolateral (ML; b and d) directions at different frequencies. Frequencies are presented on a log scale (base 10), and mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz).

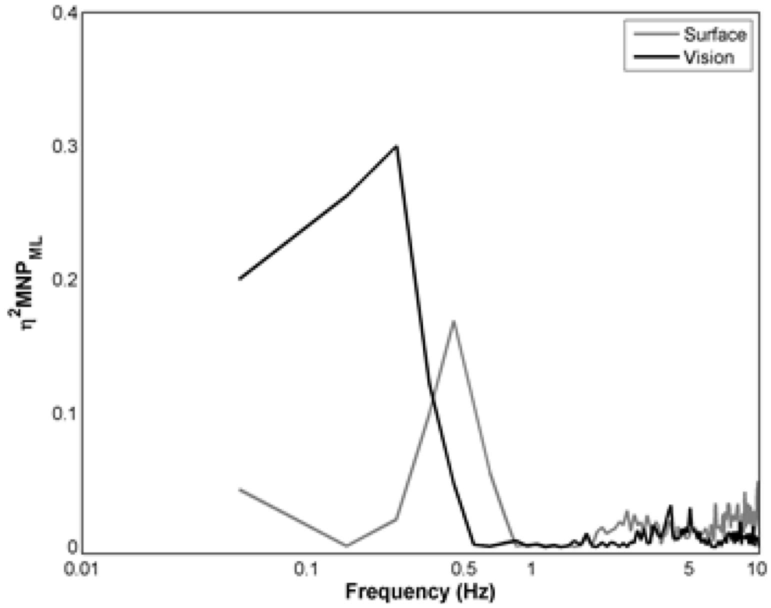

Figure 3-9: Effect sizes (η^2) corresponding to the influences of surface, and vision on the spectral content of sway in the medio-lateral direction

Mean normalized power (MNP) in the anteroposterior (AP; a and c) and mediolateral (ML; b and d) directions at different frequencies. Frequencies are presented on a log scale (base 10), and mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz).

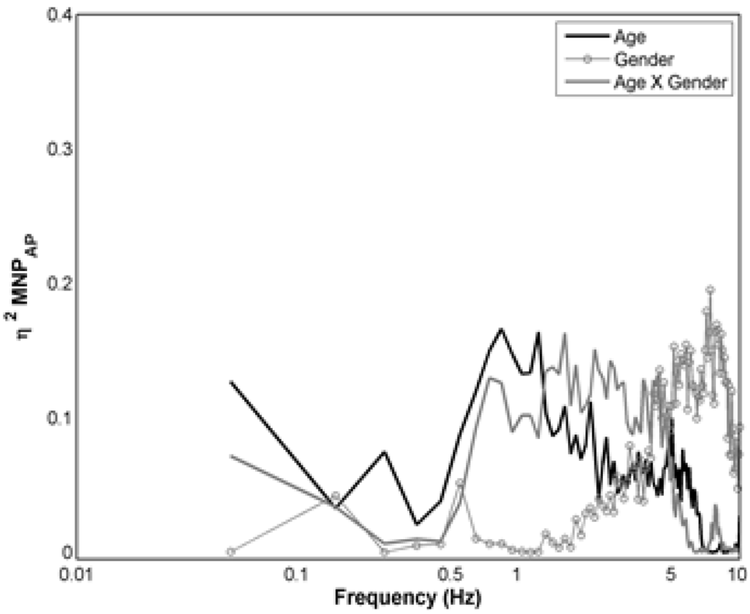

Figure 3-10: Effect sizes (η^2) corresponding to the influences of age, gender and the age x gender interaction on spectral content of sway

Mean normalized power (MNP) in the anteroposterior (AP; a and c) and mediolateral (ML; b and d) directions at different frequencies. Frequencies are presented on a log scale (base 10), and mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz).

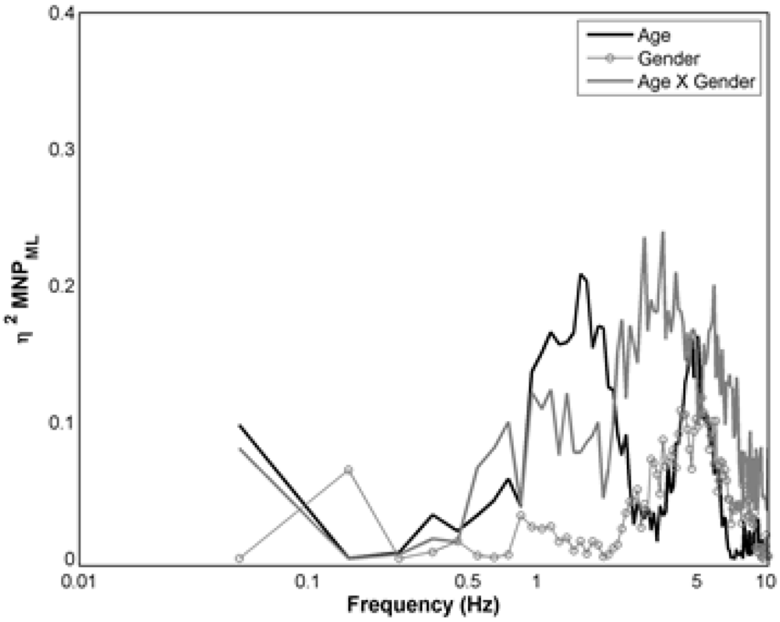

Figure 3-11: Effect sizes (η^2) corresponding to the influences of age, gender and the age x gender interaction on spectral content of sway

Mean normalized power (MNP) in the anteroposterior (AP; a and c) and mediolateral (ML; b and d) directions at different frequencies. Frequencies are presented on a log scale (base 10), and mean normalized power is displayed at the center of each spectral band (width = 0.1 Hz).

3.5 Discussion of the effects of visual and somatosensory conditions on spectral content of postural sway

Understanding the mechanisms and strategies used in controlling posture opens perspectives for evaluating the effectiveness of the postural control system to efficiently integrate diverse afferent inputs and generate required motor commands. In this study, we have assessed the relative effects of some internal (age and gender) and external (vision and surface compliance) factors on the spectral content of COP time series during quiet standing. The results suggest that visual input influences corrective responses predominantly for the control of antero-posterior sway at almost all frequencies, whereas surface compliance directs responses mostly for the control of lateral sway at middle and high frequencies. Furthermore, main effects of age and interactive effects of age with gender were larger as well as more distributed across all frequencies of sway in the medio-lateral compared to the antero-posterior directions.

Age-related deteriorations in balance have been documented in several studies using static posturography, and include increases in sway velocity, RMS distance, and mean power frequency [174]. Older individuals here swayed with higher frequency components in both directions as indicated by the spectral content reorganization. Furthermore, evidence here suggests that the spectral content of sway varied little with aging among females (Figure 1), but males produced a considerable increase in frequencies in both the ML and AP directions. This may be a result of males adopting a balance strategy involving more proximal muscle activation with age. Earlier evidence also supports a gender difference in sway performance among older adults [182], with males having a larger sway during conditions of visio-vestibular conflict.

A major challenge when examining the effects of somatosensory inputs on PCS is that these inputs stem from multiple sources, leading to a variety of approaches that have been used to assess these effects [24,36,137,176,177,183,184] but producing seemingly consistent results in that perturbing somatosensory information leads to increased postural sway [36,137,177,183]. However, the frequencies reported to reflect somatosensory modulation of sway seem to be inconsistent [126,178]. Here, introducing a compliant surface (Figure 2; Left) led to spectral content reorganization, mostly at frequencies between 0.3 and 0.8 Hz in both the AP and ML directions. Such an effect is consistent with previous studies [177,178], and suggests that medium-high sway frequencies in both directions are linked with somatosensory inputs. Moreover, a consistent effect of surface compliance was also noted at high frequencies (ranging between 4 and 7 Hz) in only the medio-lateral direction (Figure 1 & Figure 4). The effects of surface compliance were also larger as well as more extensive in the medio-lateral as compared to the antero-posterior direction. The effect sizes for surface compliance, however, were relatively small, which may have been due to the low thickness (2.3 cm) of the compliant material used [36]. These findings, nonetheless, indicate that the introduction of a surface compliance may lead to high frequency responses from musculatures that are predominantly linked with lateral control of sway.

Previous reports appear to be inconsistent in that visual feedback: 1) influences only the low frequencies of postural sway (≤0.5 Hz) [178]; 2) has an effect over the entire spectrum [33,98,126]; or 3) affects posture in two distinctly different frequencies [137]. In the present study, vision affected spectral content in nearly all frequencies (up to 9 Hz) in the AP direction; however, in the ML direction, the effect was evident only at low-middle frequencies (≤1 Hz) and at higher frequencies (>3 Hz). Our results (Figure 3-2, Figure 3-4 and Figure 3-7) suggest that all three reported characteristics of sway resulting from visual input may indeed be correct, and also confirm the co-existence of different balance mechanisms occurring at different timescales. This is consistent with the concept of slow reorientations at <2 Hz together with rapid stabilizations at >4 Hz, among others [84,137,185]. Here, a relative reduction in power in the lowest frequency band (0.1 Hz) was accompanied by increases in power at higher frequencies. These results are in agreement with previous findings that report an increase in total spectral power [33] or increase in power in the middle-higher frequencies in both directions in the absence of vision [137]. Furthermore, the findings presented here also indicate that vision had a more pervasive and stronger effect on variability of sway in the AP than the ML direction (Figure 3-2, Figure 3-4 and Figure 3-7). This would imply that vision is predominantly linked with the ankle strategy (i.e. control using distal musculature) for maintaining balance.

A “stiffening” of the musculoskeletal system [81,82,179] supports the combined ankle and hip strategy explanation. Based on a postural control model, increased system stiffness and damping lead to decreases in sway displacement and increases in sway velocity [82]. A report comparing local dynamic stability parameters among old and young adults showed faster divergence rates for older individuals, suggesting that older adults exhibited faster responses to a local perturbations [179]. Increased muscle activity, in both ankle and hip musculatures, was likely used to "stiffen" the musculoskeletal system in order to compensate for the increased compliance in the distal musculo-tendon complex especially in the elderly [83]. Furthermore, analysis of absolute spectral power (results not presented here) from the same sway data suggested that higher frequencies (>3 Hz) were associated with larger power spectral amplitudes for elderly individuals as compared to their younger counterparts, which is reportedly associated with changes in postural strategy with tendency towards increased high-frequency – lower amplitude body sway in patients with phobic postural vertigo [186]. This "stiffened" response of the postural control system, reported here and elsewhere, in the absence of sensory inputs or with age, that results from increased co-contraction, can explain the proportional reoganization of the spectral content of sway.

Another explanation for the results here might well be due to the use of different postural strategies (i.e., ankle, hip, or combination strategy) to maintain balance [24,81]. The ankle strategy works by repositioning the center of the vertical force, using moments produced at the ankle joint (and thus the distal/calf musculatures) being the primary stabilizers, whereas the hip strategy works by exerting horizontal shear forces against the surface via hip motions (and thus the proximal/hip musculatures) [24]. The ankle strategy predominantly regulates sway in the AP direction whereas the hip strategy regulates ML sway [24]. To compensate for insufficient ankle torque, it is possible that the hip ab/adductors are recruited to assist the ankle in/evertors. In other words, older individuals may opt for a combined ankle and hip strategy by activating muscles in the ankle and hip, probably by increased activation in both musculatures, instead of a pure single-joint strategy during the maintenance of posture, resulting in rapid corrective actions [24,81].

Finally, information regarding the distribution of variability at different frequencies would not only help in distinguishing between the effects of various sensory modalities on sway but also in designing patient-specific rehabilitation programs that are aimed at improving balance. Differences in the spectral content of sway could potentially be used to diagnose aspects of the PCS or the sensory system that could be contributing to balance problems in a particular individual. In a clinical setting, if sway measurements conducted on a patient (or an individual), show differences in the spectral content over frequencies in the middle ranges, e.g. 0.4 – 0.7 Hz (Figure 3-7, Figure 3-8, Figure 3-9), then it might suggest impairments associated with the somatosensory system. In addition, spectral content of medio-lateral and antero-posterior sway seems to be more sensitive to changes in the somatosensory and visual input respectively, in both range as well as magnitude (Figure 3-7, Figure 3-8 and Figure 3-9). Thus, information regarding the spectral content and variability of sway bi-directionally at different frequencies may help improve the application of sway measurements in a clinical setting by distinguishing the effects of different sensory modalities.

4. Extreme levels of noise constitute a key neuromuscular deficit in the elderly

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4.1 Summary of neuromuscular noise and variability during task performance

Fluctuations during isometric force production tasks occur due to the inability of musculature to generate purely constant submaximal forces and are considered to be an estimation of neuromuscular noise. The human sensori-motor system regulates complex interactions between multiple afferent and efferent systems, which results in variability during functional task performance. Since muscles are the only active component of the motor system, it therefore seems reasonable that neuromuscular noise plays a key role in governing variability during both standing and walking.

Seventy elderly women (including 34 fallers) performed multiple repetitions of isometric force production, quiet standing and walking tasks. No relationship between neuromuscular noise and functional task performance was observed in either the faller or the non-faller cohorts. When classified into groups with either nominal (group NOM, 25th – 75th percentile) or extreme (either too high or too low, group EXT) levels of neuromuscular noise, group NOM demonstrated a clear association ($r2>0.23$, $p<0.05$) between neuromuscular noise and variability during task performance. On the other hand, group EXT demonstrated no such relationship, but also tended to walk slower, and had lower stride lengths, as well as lower isometric strength. These results suggest that neuromuscular noise is related to the quality of both static and dynamic functional task performance, but also that extreme levels of neuromuscular noise constitute a key neuromuscular deficit in the elderly.

4.2 Introduction to variability during task performance and noise

The order of recruitment as well as the variability in the firing of multiple motor units during voluntary isometric submaximal muscular contraction results in an inability of the musculature to generate constant forces, causing oscillations or fluctuations in the resulting force output [22,54,58,152,160,168,187]. The level of force fluctuation is thus modulated by physiological parameters such as the number, size and discharge rates of the motorneurons, as well as muscle fiber type etc. [22]. Due to these physiological characteristics, the level of fluctuation during isometric force generation is considered to be an approximation of the amount of neuromuscular noise, considered to be disturbances that obscure the desired output of the sensorimotor system [48,51,58]. Furthermore, neuromuscular noise is known to be proportional to the force output [188]. The variability of kinetics and kinematics are therefore dependent upon the requirements of the task, such that e.g. final location accuracy is reduced with increasing trajectory speed [47,188].

Since this variability within the generated force is known to influence the intended movement trajectory [41,42,47,160], the presence of neuromuscular noise is thought to affect the trial-to-trial repetitions of a task [22,188]. The effective regulation of neuromuscular noise is therefore a prerequisite for continuous or repetitive functional task performance, such as standing (postural sway) and walking (gait variability) [19,30,47,121]. The level of force fluctuations during muscular contractions [22,117,152,160] thus needs to be accounted for in order to optimize kinetics and kinematics during task performance, and this is achieved through feedback mechanisms within the sensori-motor system [17,19,22,30,47,81,189,190]. It is reasonable that variability during repetitive tasks provides a measure of an individual's static or dynamic task performance, and could be used to assess the limitations of their system. The quantification of variability during task performance has therefore become a target for evaluating the human sensori-motor system [19,21,27,68,91,160,174,191,192].

Variability during task performance is omnipresent and does not necessarily suggest motor related pathology [27,121]. In fact, variability is an indicator of redundancy within the system that allows performance adaptation, and is therefore thought to be necessary for optimized task learning [122,123]. On the other hand, excessive variability may indicate that the system is operating closer to the limits of ability, expressed as stability during balance and gait [68,70,90,91,121,192]. Here, in order to maintain stability, the center of mass must be effectively maintained within the base of support. A stable system during standing would therefore either stay in or return to a state of equilibrium after being perturbed [21,79]. In a similar manner, during dynamic conditions e.g. walking, a stable system would remain in a state of uniform motion, maintained by suitable foot placement. Systems with higher levels of variability would thus require greater error correction in order to maintain the center of mass within the base of support. In fact, higher levels of variability during standing and walking, have been observed in individuals that are at increased risk of falling, as well as in those who suffer from motor related pathologies [70,174,192]. Until now, variability during static or dynamic functional tasks has been viewed independently [17,21,81,91,193,194], but it seems plausible that variability during specific tasks results from core system characteristics such as neuromuscular noise, together with local functional ability, including strength, coordination and training of the specific musculature. Since muscles are the only active component of the motor system, it seems reasonable that neuromuscular noise in the lower extremities could explain variability during upright (standing posture) tasks including standing and walking. An understanding of the contribution of force fluctuations, as a measure of neuromuscular noise, on balance and walking performance in elderly populations would not only help to provide an understanding of the etiology of postural sway and gait variability, but might also aid in the early diagnosis of motor related pathologies, particularly in individuals with balance and gait deficits. The aim of this study was therefore to investigate the relationship between neuromuscular noise and static and dynamic task variability among elderly healthy and faller cohorts.

4.3 Methods to test the relationship between neuromuscular noise and task variability

4.3.1 Participants

Within a larger study examining the risk of fracture in the elderly (EU VPHOP FP7–223864), we examined ninety elderly participants from the local community. Of these 90, a number of subjects who reported conditions of arthritis, artificial joints, diabetes and/or herniated vertebral discs were excluded from the study cohort for this analysis. As a result, seventy elderly women (34 with at least 1 fall within the previous 12 months - “faller”; 36 healthy controls – “non-faller”) undertook the experimental protocol. All participants provided written informed consent and the experiments were approved by the local ethics committee. Both groups were homogenous in terms of age, weight and height with a mean (± SD) of: 69.8 (± 4.8) years, 69.7 (± 10.2) kg and 163.1 (± 6.6) cm for elderly fallers, and 69.2 (± 4.6) years, 67.7 (± 10.7) kg and 162.1 (± 6.0) cm for elderly non-faller cohorts respectively.

4.3.2 Experimental Design and Procedures

Within each test session, participants performed a minimum of 3 test repetitions or trials to examine force fluctuations, postural sway, and walking variability in separate sessions conducted on the same day. Force fluctuations were measured on the right limb during isometric knee extension and isometric ankle plantar-flexion. Postural sway was measured during quiet standing in a biped position with eyes open. Gait assessment was performed at preferred walking speed.

4.3.3 Force fluctuations measurements

In this study, force fluctuations were considered an indirect measure of neuromuscular noise, and were assessed in the knee extensors and ankle plantarflexors. Briefly, participants were seated in a standardized position in a Biodex 3 Pro dynamometer (Biodex Medical Systems Inc., USA) [117]. Before each measurement the flexion/extension rotation axis of the tested joint was aligned with the rotational axis of the dynamometer. Knee extension measurements were then conducted with the knee flexed at 90 degrees, while for ankle measurements, the knee was fully extended with 10° of plantarflexion at the ankle. Prior to the start of each force fluctuation session, maximum voluntary isometric contractions (MVICs) were obtained by providing standardized instructions and verbal encouragement, trying to reach peak exertion 2–3 s after the start of the trial. MVICs, which lasted for 5s, were measured three times with a minimum of 30s pause between contractions [152]. The single maximum value from the three contractions for the ankle as well as the knee was then used as the respective MVIC.

Objective or target torque (TT) level was provided visually as a constant or ramp ascending torque plot. The TT was overlaid by the actual torque produced in real-time, such that both plots were displayed simultaneously on the monitor. TTs were set at constant levels of either 15% or 20% MVIC, or to a ramp ascending torque from 15 – 20% MVIC for each test joint. Participants were instructed to match the torque level as best they could for the duration of the 15s test by performing isometric knee extension or ankle plantarflexion respectively. The active torque applied by the participant was displayed as a real-time visual feedback at 10Hz, which overlaid the TT. Participants were provided 4-5 practice test repetitions to familiarize themselves with the experimental procedures. The presentation order of the signals was randomized, with all TTs (i.e. constant 15%, constant 20% and ramp of the 15-20% MVIC) presented a minimum of three times.

4.3.4 Postural sway measurements

In order to obtain measurements of postural sway, participants were requested to stand barefoot in a quiet, bilateral stance with eyes open and with their hands by their sides. In this condition, participants focused on a visual target, positioned at eye level on the wall, approximately 3m in front of them, and were instructed to stand as still as possible. The medial aspects of the tibial malleoli were positioned not more than 7 cm apart from one another, but on separate force platforms (AMTI OR6-7-1000, Watertown, Massachusetts, USA). In order to ensure the repeatability of the sway tests, foot locations were marked on the force platforms.

Participants were provided a minimum of 60 seconds practice before 3 repetitions of quiet standing were recorded. At least one minute relaxation was provided between each sway test. Tri-axial ground reaction force data were recorded at 120Hz in order to allow determination of measures of the center of pressure.

4.3.5 Gait analysis

The 3D kinematics of the right foot were measured using 4 reflective markers (14mm) attached to the skin, tracked at 120 Hz using a 10-camera motion capture system (Vicon, OMG Ltd, Oxford, UK). Using manual palpation to locate the bone landmarks, the markers were attached to the tuber calcanei (heel), caput ossis metatarsale I (first metatarsus), caput ossis metatarsale V (fifth metatarusus) and at the base of the os metatarsale II and III (at the base of the second and the third metatarsus). Participants were requested to walk barefoot along a 10m straight walkway, at their preferred walking speed, with recording beginning after at least 3 practice walks. A minimum of 6 walks were then measured for the determination of measures of gait.

4.4 Data Collection and analysis for assessing the relationship between intrinsic noise and output variability during task performance

4.4.1 Force fluctuations

All torque measurements were collected using Labview (Labview 8.6, National Instruments, Inc., USA). From each trial, the first 7 and the last 2 seconds of torque output were removed to avoid any transients during initiation or termination of the trials. All data were then low pass filtered (4th order, zero-phase lag, Butterworth, 25 Hz cut-off frequency). In order to assess force fluctuations, both mean and standard deviation of the force production signal were evaluated [117]. In addition, the coefficient of variation (CV) of the force was calculated as the ratio of the standard deviation to the mean of the force output for each type of force fluctuation test and joint.

4.4.2 Postural sway

Since all force fluctuation measurements were derived from muscles that are predominantly associated with sway in the antero-posterior (A-P) direction, all tri-axial force data for postural sway were also transformed to obtain CoP times series in the A-P direction [19], with the initial and final 2 seconds of data removed to avoid boundary effects. After low-pass filtering (Butterworth, 2nd order, bi-directional, 5Hz cut-off frequency), mean (MDIST) and root mean square (RMS) distance of the CoP time series were calculated to quantify sway [65,174] in the A-P direction. In addition, the CV of postural sway for the CoP time series in the A-P direction was calculated as the ratio of the RMS to the MDIST of sway in A-P direction.

4.4.3 Gait analysis

The trajectories of the right heel marker and the marker at the base of the second and the third metatarsus were used to extract stride time information. After low-pass filtering (Butterworth, 4th order, bi-directional, 25Hz cut-off frequency), heel strikes were identified using a foot velocity algorithm [76]. Two consecutive heel strikes were then defined as a single stride and the time elapsed between heel strikes (in seconds) provided the stride time. A minimum of 6 walks were used to calculate the variability of stride time with the first and last strides from each walk removed to avoid transients, leaving a total of approximately 30-40 strides for analysis. The CV of stride time, which represented kinematic gait variability, was calculated for each participant as the ratio of the standard deviation to the mean of the stride time for all walks.

4.5 Statistical Analyses

4.5.1 Factor Analysis for extraction of principal force fluctuation components

Factor analysis (FA), using the "FACTOR" procedure (within the SPSS statistics package), was applied to the CV of force fluctuation obtained from the three signals (constant 15%, constant 20% MVIC and ramp 15 – 20% MVIC) during ankle plantarflexion and the same three signals during knee extension. The correlation analysis method was used to extract the principal components of force fluctuation before the "VARIMAX" procedure applied the appropriate rotation. Only those force fluctuation principal components (ffPCs) that had Eigenvalues greater than one then formed the dimension of the component dataset. This reduced set of ffPCs, instead of the original six CVs of force fluctuation, were considered representative of the key aspects of neuromuscular noise, and were used to compare the levels of noise between faller and non-faller cohort groupings, as well as to examine the relationships between force fluctuations, postural sway and gait variability in all subjects.

4.5.2 Noise and variability during task performance in fallers and non-fallers

In order to assess differences between faller and non-faller cohorts, non-paired t-tests were conducted on ffPCs, CV of postural sway (in the A-P direction) and CV of stride time, with significance set at 0.05.

4.5.3 Relationship between force fluctuation, postural sway and gait variability

To examine the relationship between force fluctuations, postural sway and gait variability, two stepwise multiple linear regression (MLR) analyses were performed for each cohort, with independent variables being the derived force fluctuation components from the factor analysis. Dependent variables were firstly CV of postural sway in the antero-posterior direction, and then CV of stride time from the right limb with significance for regression analyses set at 0.05.

In the final stages of this study, we aimed to establish the relationship between force fluctuations, postural sway and gait variability. Here, since the relationship between system noise and task performance is thought to be non-linear [121], the derived components from the factor analysis were used to classify individuals into three sub-groups based on the percentiles of the distribution of the ffPCs [70], using 1st and 4th quartile (25th – 75th percentile) groupings. In this approach, individuals with noise levels within 2nd and 3rd quartiles were termed the nominal noise level group (group NOM), while those outside these bounds were considered the extreme noise level groups (group EXT). The relationships between local noise components, postural sway and gait variability, were assessed within these sub-groups using MLR analyses.

The significance for regression analyses were set at 0.05. All statistics were conducted using the SPSS package (SPSS v20, IBM Corp., USA). Furthermore, to ensure comparability of results, all values of ffPCs, postural sway and gait variability were converted and presented as standardized Z-scores.

4.6 Results of the relationship between neuromuscular noise and variability during task performance

4.6.1 Factor Analysis for extraction of principal force fluctuation components

The derived dimension of the force fluctuation dataset was two, representing the key components of the original force fluctuation data, with Eigenvalues of 2.7 and 1.2 (Table 4-1). The rotated component matrix (Table 4-2) indicated that ffPC 1 was predominantly associated with force fluctuations from the ankle plantarflexors, and this component was therefore denoted "ankle noise", while ffPC 2 was almost entirely composed of force fluctuations from the knee extensors, and hence termed "knee noise".

Table 4-1: Correlation coefficients for force fluctuation datasets for all participants

Figures in bold show significance at $p < 0.05$, while * indicates $p < 0.01$.

	CV Ankle 15%	CV Ankle Ramp	CV Ankle 20%	CV Knee 15%	CV Knee Ramp	CV Knee 20%
CV Ankle 15%		**0.34***	**0.50***	0.25	**0.22**	**0.33***
CV Ankle Ramp			**0.70***	0.02	**0.41***	**0.27**
CV Ankle 20%				**0.22**	**0.34***	**0.28***
CV Knee 15%					**0.35***	**0.52***
CV Knee Ramp						**0.32***
CV Knee 20%						

4.6.2 Noise and variability during task performance in fallers and non-fallers

4.6.2.1 Force fluctuations

The faller cohort performed the torque generation task with higher levels of knee noise than their non-faller counterparts ($p < 0.05$, Table 4-3). However, no significant differences were observed between the faller and non-faller cohorts for ankle noise.

Table 4-2: Noise components

The two derived and rotated principal components indicate that the first component (Eigenvalue = 2.7) was composed of force fluctuations from the ankle plantarflexors and has thus been renamed "*ankle noise*", while the second component (Eigenvalue = 1.2) represented force fluctuations from the knee extensors, renamed as "*knee noise*". The rotated components ankle and knee noise are presented in standardized (*Z*-scores) values.

	PC 1: Ankle noise (Eigenvalue = 2.7)	**PC 2: Knee noise (Eigenvalue = 1.2)**
CV Ankle 15%	**0.59**	0.32
CV Ankle Ramp	**0.90**	0.00
CV Ankle 20%	**0.88**	0.15
CV Knee 15%	0.00	**0.90**
CV Knee Ramp	**0.45**	**0.48**
CV Knee 20%	0.22	**0.78**

4.6.2.2 Postural sway

During quiet standing, faller cohorts exhibited significantly higher values for CV of sway in the antero-posterior direction compared to the non-fallers ($p = 0.02$, Table 4-3).

4.6.2.3 Gait variability

The CV of stride time was approximately 44% higher for the fallers compared to the non-fallers ($p = 0.03$, Table 4-3).

4.6.3 Relationship between force fluctuation, postural sway and gait variability

MLR analyses found no association for fallers or non-fallers between *ankle* and *knee noise*, and postural sway or gait variability. However, classification (Figure 4-1) into *nominal* (group NOM, 24 participants aged 68±5 years) and *extreme noise level groups* (group EXT, 46 participants, aged 70±5 years), revealed a non-linear relationship between noise and task performance (Figure 4-2) as follows:

Table 4-3: Differences between faller and non-faller cohorts in variability during task performance

Force fluctuations were quantified using the coefficient of variation (CV), of the force production signals with TTs set at 15%, 20% and 15 – 20% ramp for ankle plantarflexors and knee extensors. CV of postural sway in the A-P direction was evaluated as the ratio of the RMS of sway to the mean distance of sway in the A-P direction. Finally, gait variability was quantified using CV of stride time during walking from the right leg. Values in bold represent significance with $p < 0.05$, while * represents significance at $p < 0.01$.

		Non-fallers (N = 36)	Fallers (N = 34)
Force fluctuations	Ankle noise	0.01 (± 0.90)	-0.1 (± 1.11)
	Knee noise	**-0.22 (± 0.74)**	**0.23 (± 1.2)**
Postural sway	CV Sway A-P	**-0.25 (± 0.69)**	**0.26 (± 1.2)**
Gait variability	CV Stride time	**-0.32 (± 0.90)***	**0.34 (± 1.0)***

In group NOM, there was a significant relationship between *knee noise* and CV of postural sway in Z-score values ($r^2 = 0.23$, $p = 0.02$, Figure 4-2).

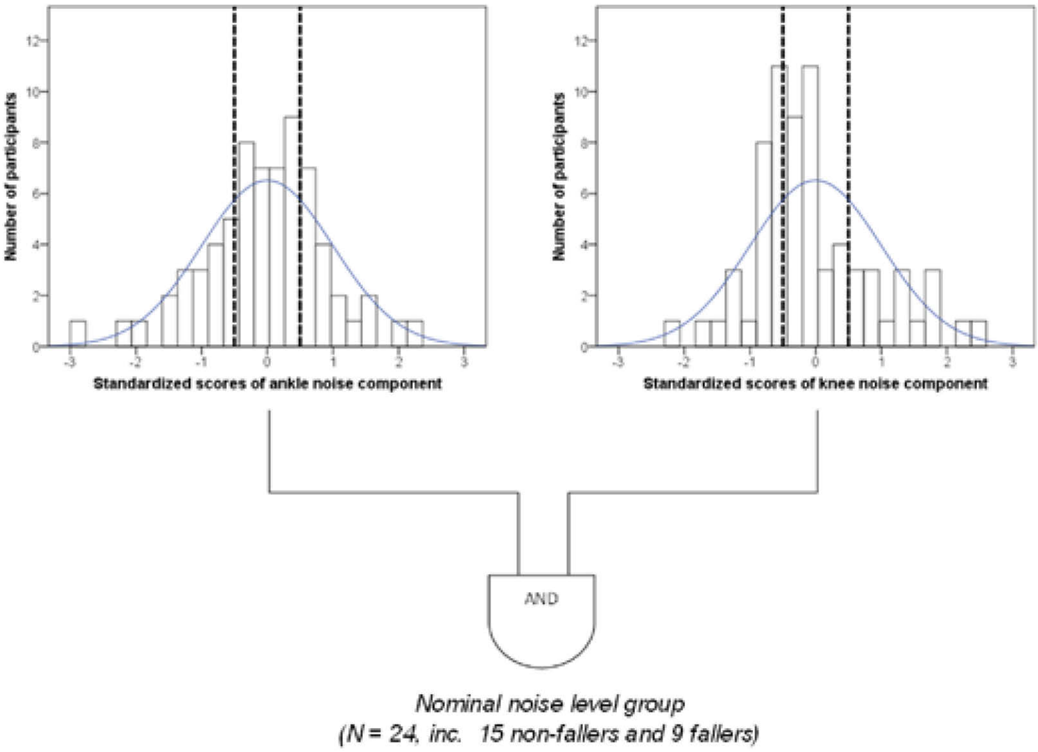

Figure 4-1: Classification of participants based on levels of neuromuscular noise

Histogram of the 1st and 2nd rotated components obtained using the factor analysis, representing the ankle and knee force fluctuations, or "ankle noise" and "knee noise" respectively. The dotted lines represent the 25th and the 75th percentile boundaries. The bell shaped curve illustrates the normal distribution plot for the knee as well as the ankle noise components. The participants that had both ankle noise and knee noise values inside the dotted lines (25-75th) were classified in the nominal noise level group (group NOM, N = 24, inc. 15 non-fallers and 9 fallers), while those that had values outside the dotted lines formed the extreme noise level group (group EXT).

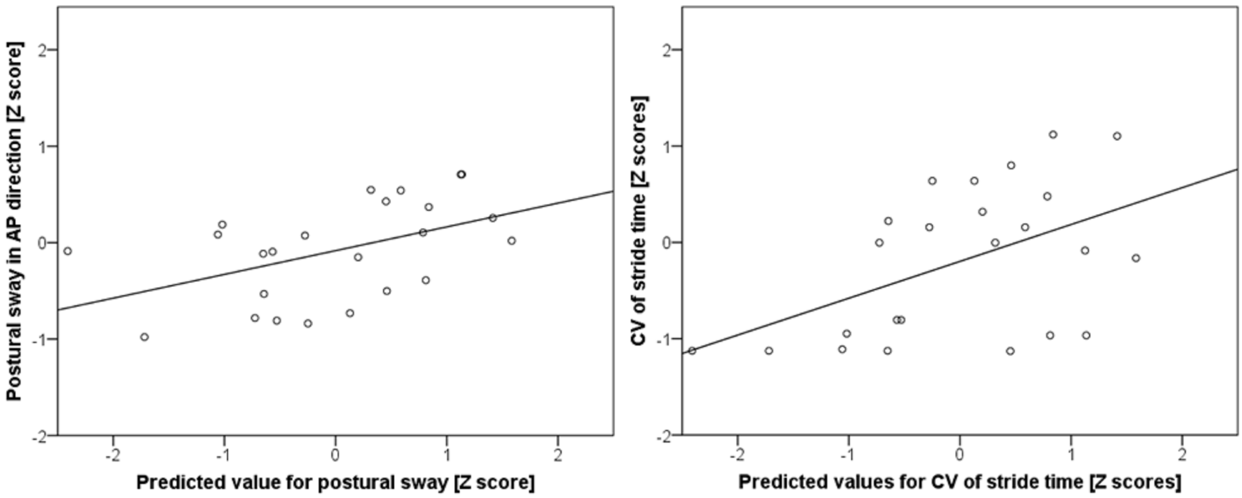

Figure 4-2: The relationship between neuromuscular noise and variability during task performance

The regression plots for group NOM using standardised Z-scores of the measured postural sway in AP direction (Figure 2; Top) and stride time variability (Figure 2; Bottom) represented on the y-axis against standardised Z-scores of the predicted values from the regression with independent variables as ankle and knee noise. The r^2 for the regression with postural sway in A-P direction as dependent variable was 0.23 and with stride time variability was 0.24.

4.7 Discussion of the relationship between neuromuscular noise and variability during static as well as dynamic task performance

Variability during task performance is known to be increased in subjects who have fallen [40,41,90], but the etiology of variability during static and dynamic functional task performance has until now, remained unclear. Based on the notion that the fluctuations during isometric force production tasks closely represent neuromuscular noise [30,47,58,152], this study examined whether levels of neuromuscular noise could predict variability during standing and walking. In this study we therefore investigated the levels of, as well as the relationships between, neuromuscular noise in the knee extensors and ankle plantar-flexors, and variability during task performance in cohorts of fallers and non-fallers. The results of this study indicate that fallers possess higher levels of noise during muscular force production in the knee extensors ($p<0.05$) but not in the ankle plantarflexors. In addition, fallers also exhibited higher levels of postural sway and gait variability than their non-faller counterparts. We observed that subjects with nominal levels of neuromuscular noise throughout the lower extremities (group NOM) exhibited a clear association ($r2>0.23$), whereas those with extreme (high as well as low) noise levels (group EXT) did not. In addition, group EXT possessed lower stride lengths, isometric muscle strengths and walking speeds. This suggests that extreme levels of noise during force production in the lower extremities are associated with functional deficits consistent with reduced gait stability [40,41,68] and even falling [21,69,90,195], and could therefore be considered a key neuromuscular deficit in the elderly.

Excessive levels of variability during standing as well as walking are factors known to limit functional performance in the elderly [68,70,88,90,121,192]. However, recent studies indicate that nominal levels of variability might be essential for effective task learning [27,122,123], while extreme levels of variability, both high and low, might indicate motor-related pathologies [68,69,70,90,121,191]. Our premise in this study was that neuromuscular noise is responsible for the variability in output task performance. This was demonstrated in our study by a clear relationship between noise in the knee extensors and variability during standing and walking in subjects with nominal levels of neuromuscular noise. However, no such relationships were present in subjects who exhibited excessively high or extremely low levels of noise, suggesting either some compensation mechanisms or neuromuscular deficits. Such adaptations might well be due to a remodeling of the sensori-motor system in these individuals, possibly also leading to the observed lower levels of isometric strength in the knee extensors and shorter strides, as well as a tendency towards slower walking.

In order to avoid excessive levels of variability that could lead the system either to operate closer to or even outside the limits of stability during continuous standing or walking, the human sensori-motor control system attempts to regulate and maintain the center of mass within the base of support by using a variety of strategies [17,21,26,81,89,190,193,195,196]. The results of this study suggest not only that the quality of control of posture and movement, but also the choice of control strategy seems to be influenced by the level of noise in the sensori-motor system. Since fluctuations during force production at the knee were a predictor of sway and gait variability in group NOM, it seems that one mechanism for effective task performance, at least in these subjects, might well have been a strategy involving optimization of neuromuscular noise in the force outputs [30,47]. While the exact mechanisms remain unclear, it appears that effective regulation of neuromuscular noise within the sensori-motor system might be a prerequisite for improved task performance.

Fluctuations in force generation during submaximal isometric contractions within a particular muscle are known to be dependent upon the discharge properties of the motor units recruited to perform the required task [22,54]. However, variability during task performance such as standing or walking, depends not only the recruitment of motor units within a particular muscle, but also on other factors such as muscle force-length and force-velocity relationships [197], muscle coordination [198], sensori-motor feedback quality [143], and alternating activation of agonist, synergists and antagonists [17,22,40,42,81,194,196], as well as the requirements of the task itself [42,144,187]. For example, task performance during position-matching (anisometric) activities is thought to differ from performance during position-maintaining (isometric) tasks [42,144,187]. While many of these complexities could not be specifically considered within our study, the underlying mechanisms governing the variability of output task performance seem to be closely associated with the levels of neuromuscular noise. Further support for such a concept comes from studies that show a clear relationship between the variability in discharge properties of active motor units, and the task performance, including the variability of force output [42,144,187]. Furthermore, it is important to note that in this study, fluctuations were measured at 15 – 20% MVIC, but it is possible that fluctuations at different recruitment levels might also play a role in sway during standing [125], as well as in variability during walking. It is therefore plausible that assessment of different aspects of neuromuscular noise, including different contractions as well as at varying force levels, might allow a more comprehensive understanding of the relationships between neuromuscular noise levels and task performance. On the other hand, according to the Optimal Control Theory proposed by Harris and Wolpert [30,47], which suggests that SD and mean of the produced force are proportional, the relationship between neuromuscular noise levels and variability during task performance should be independent of the force production levels. Further investigation is therefore required in order to provide a deeper understanding of the in vivo relationships between force levels, the recruitment of motor units, variability of discharge rates of the active motor neurons, and the quality of task performance [42].

While a variety of both clinical and functional approaches have been used to investigate the risk of falling in the elderly (for an overview see [90,199]), we have addressed the role of the underlying physiological characteristics, specifically neuromuscular noise, on task performance in these populations. In this study, we examined the relationships between force fluctuations, postural stability and gait variability in faller and non-faller cohorts. Elderly fallers are known to possess higher levels of sway [174], as well as increased gait variability [68,90,91,191], than their non-falling counterparts, and this has been confirmed in our cohorts (Table 1). In this study, fluctuations during force production were larger in elderly fallers compared to non-fallers and this deficit might have affected the control of both the timing of stride events during walking as well as sway during standing. More importantly, for the first time, it was demonstrated in this study that neuromuscular noise levels might play a direct role in the quality of both static and dynamic functional task performance. Specifically, individuals with nominal levels of noise exhibited a clear association between neuromuscular noise and variability during task performance. On the other hand, individuals with extreme levels of noise, did not exhibit any such relationship, but also tended to be older and walked slower, while having lower isometric strength in the knee extensors and smaller stride lengths. Although further investigation is required, it seems reasonable that an assessment of force fluctuations in the musculature of the lower limb, achievable in a clinical setting, could contribute towards the early identification of motor related pathologies. Whether intervention programs or clinical therapies to improve muscular control and steadiness are then able to also reduce e.g. a subject’s risk of falling, remains to be elucidated.

4.8 Conclusions of neuromuscular noise and variability during task performance

Individuals with nominal levels of noise exhibited a clear association between intrinsic neuromuscular noise, assessed as force fluctuations from muscles of the lower extremity, and the quality of performing both static and dynamic functional tasks. However, in individuals with extreme levels of neuromuscular noise, no such relationships were observed and these subjects possessed neuromuscular compensations such as lower stride length and isometric strength. The results of this study therefore suggest that extreme levels of neuromuscular noise, both excessively high and low, constitute a key functional deficit in elderly individuals.

5. General Discussion

With a progressive increase in the proportion of elderly within the western population, the increase in the occurrence of falls, injuries and other age related movement disorders is a major cause of socio-economic concern for health care organizations. Thus, there is a clear need to address the issues of age, fall and other neuro-degenerative diseases that affect the geriatric population. Recent research suggests that assessment of variation during task repetitions is critical for understanding age-related functional adaptation of the human sensorimotor system [25,27,30,47,49,50]. Here, it seems that quantification of variability during task performance is not only sensitive for identifying fall-prone individuals [43,90,91,121], but can also aid in early detection of neuro-degenerative disorders that affect the geriatric population such as Parkinson's or Huntington's disease [13,14,64].

In order to be able to perform any task successfully, the human sensorimotor system, among other things, needs to control the timing and coordination of multiple muscles, while continually maintaining the system under balanced conditions. However, due to multiple redundancies as well as complexities present in the human sensorimotor system, a constant level of task performance is not possible [25,27,30]. Instead, variations in repetitions of tasks are observed. These inter-trial variations are not stochastic but are rather a function of the level of neuromuscular noise present within their sensorimotor systems [25,47,49]. The assessment of such trial-to-trial variations during task performances such as force production, as well as standing and walking, have been found to be relatively successful in identifying motor related pathologies. However, the translation of these assessments either remains limited or in certain cases even elusive in clinical settings [90,93]. If quantification and assessment of variability during task performance can be helpful in accessing the functioning of the sensorimotor system as well as providing means for early identification of motor related pathologies, then consideration of such indices could complement clinical decision making. However, the controversies associated with the interpretation of some of the findings related to intra-subject variability during task performance are a key barrier towards implementation of such assessment in the clinical setting. Although pathological and perturbed systems have shown larger levels of variability in comparison to the controls, increased levels of variability does not necessarily suggest a systemic deficit [27,70,121]. Thus, the main aim of this dissertation was to elucidate the contribution of intrinsic as well as extrinsic perturbations on static as well as dynamic task performances by assessing the trial to trial variations in the multiple task repetitions.

The variations during task repetitions including cohorts of young and elderly as well elderly fallers undertaken within this dissertation, establish the efficacy of these measurements for use in clinical settings for deeper insights into the performance of the human sensori-motor system. Here, tasks were performed on a local as well as a global level in a step-by-step manner in order to establish whether:

- trial-to-trial variations can be measured in a repeatable manner from the lower extremity muscles
- fatigue related changes during force production tasks not only include increased fluctuations and inaccuracy, but also that the force produced after the onset of fatigue possesses larger levels of physiological tremor
- introduction of a compliant surface during static standing tasks leads to spectral changes in the medio-lateral direction, while the absence of vision leads to spectral changes in the antero-posterior direction
- the spectral content of static standing revealed distinct rhythmic patterns while perturbing the visual and somatosensory systems, with somatosensory inputs predominantly operating at mid-frequency ranges, while visual inputs mostly operated at either very low or very high frequencies
- individuals that experienced a fall exhibited higher levels of variability during force production, static standing and walking
- there is a non-linear relationship between neuromuscular noise and variability during task performance.

The variability or fluctuations during isometric force production from the knee extensors not only revealed high levels of both inter- and intra-session reliability, but also indicated an increase in force fluctuations post-fatigue among a group of healthy young adults (cf. Chapter 2 for details). Both of these results confirmed our hypotheses on whether fatigue will lead to an increased variability and shift in power spectral profiles towards higher frequency content, demonstrating fatigue related modifications in task performance. Here, the onset of fatigue is known to render the muscle unable to generate the desired force output [200]. If the particular task is sustained, this probably requires increased activation of the Ia afferents (excitatory sensory receptors) leading to either the recruitment of new MMUs (larger units as per the size principle) or readjustment of the firing rates of the already recruited MMUs [37,113,118,133,200]. Both these scenarios lead to changes in the human *stretch reflex arc*

(Figure 5-1). A *stretch reflex* is a rapid response produced by a muscle when it experiences a brief stretch or an increase in length [61,131,132,201,202]. Stretch reflexes have been observed during the analysis of not only whole-body task performances such as standing, walking, running or landing, but also during fine motor tasks [61,131,132,201,202]. Furthermore, inducing muscle fatigue via sustained activity and/or contraction modifies the chemical as well as the mechanical properties of the muscle [113,200,203,204] as well as the stretch reflex arc [37,133,205]. The increased variability in the force output, which can be explained by the fact that neuromuscular noise depends on the magnitude of the signal (in this case increased activation of the excitatory Ia afferents Figure 5-1, of the human *stretch reflex arc*) leading to larger fluctuations or variability in the force output [39,118]. Missenard and colleagues [118], however, have also reported larger levels of force variability post-fatigue in situations when their participants were requested to maintain the same levels of activation. This finding led the authors to rule out the possibility of increased activation of the Ia afferents (increased excitatory signaling) as the only contributor towards large force output variability [118]. Based on the aforementioned finding, the authors theorized that the increased fluctuations in force output post-fatigue could also be due to the increased inhibitory activity of the group III and IV afferents largely resulting from the chemical changes imposed by the onset of fatigue [200,206]. Furthermore, the observed increase in the contribution of tremor related frequencies suggests modifications in the structure of the generated force, post-fatigue. Elble and Randall [142], for example, suggested that spinal segmental stretch reflex might lead to such oscillations, and used the time lag from EMG for development of the movement detectable by the afferent receptors to corroborate their findings [72,131]. The authors suggested that a spinal segmental reflex time in the finger of 50 ms, implies a 50 X 2 = 100 ms loop time, will directly translate into an oscillatory pattern with a period of 0.1 s or 10 cycles/s, 10 Hz [72,131]. These changes suggest increased overall sensitivity of the stretch reflex arc [37,133,145,207] as well as the rhythmic modulation of multiple MMUs [50,57,59,62,118,131,132,206]. Thus, these results aid in understanding not only the fatigue related modifications induced during force production, possibly due to increased a) excitatory activation of either Ia afferents or b) inhibitory activation of III or IV afferents c) rhythmic modulation of the recruited MMUs, but also the increased variability during task performance as well as fall risk among elderly individuals [110].

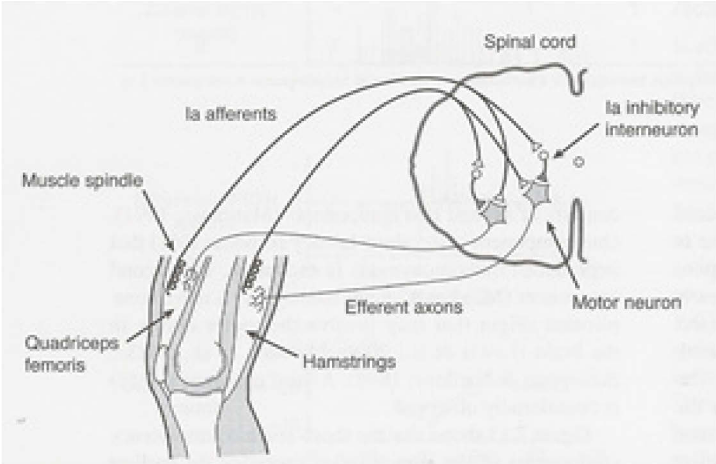

Figure 5-1: A schematic presentation of the human stretch reflex arc adapted from Enoka and Duchateau [112]

Oscillations in this arc have been argued to affect the spectral content of the force production tasks which have been observed in both the electromyographic as well as the task output recordings.

In a similar manner to the force production tasks, the assessment of oscillatory patterns of variability during quiet standing or sway, suggested age-related changes in the structure of variability (sway) occurred mostly in the medio-lateral directions, while changes due to perturbations to the visual input during standing for all healthy adults manifested themselves mainly in the antero-posterior direction (see Chapter 3 for details). These results provide confirmation that the strategies for maintenance of balance during standing in the antero-posterior and medio-lateral directions are almost entirely independent of each other [17,19,81]. Thus, both these studies (included in Chapters 2 and 3) clearly demonstrate that the variability during task performance is sensitive in identifying and highlighting functional adaptations resulting from both intrinsic (due to fatigue, aging as well as motor-related pathologies) as well extrinsic (due to changes in the environment such as visual or surface conditions) factors.

Increased postural sway [7,67,92,146] and gait variability [43,68,91,121] among fallers has previously been observed in many studies. However, most investigations are limited in scope as intra-subject variability during standing and walking have been interpreted independently of each other. In fact during both standing and walking, the human sensorimotor system applies feedback control mechanisms to maintain the whole-body center-of-mass within the base-of-support in order to ensure effective performance of the task. As the human sensorimotor system is noisy, it is likely that this noise is exhibited during task performance. The role of neuromuscular noise on the intra-subject variability during static and dynamic tasks could clarify the interpretation of trial-to-trial variations during task performance. Thus, the primary goal of this dissertation (cf. Chapter 4) was to understand the relative contribution of neuromuscular noise on variability during both static as well as dynamic task performance. Here, 70 elderly females from the local community were recruited within this study (cf. Chapter 4 for details) firstly, to assess the levels of intra-subject variability during task output. Here, we found that elderly adults that had experienced a fall in the 12 months prior to data collection ("fallers") showed larger levels of fluctuations in force production tasks, sway during standing and kinematic variability during walking as compared to their age-matched healthy counterparts, "non-fallers" (see Chapter 4 for details). This finding our proposed hypothesis and provided evidence that "fallers" might have a motor-related disadvantage, requiring larger corrections by their sensorimotor systems. Secondly, in order to understand the relationships between neuromuscular noise and variability in the task output, we examined the relationship between fluctuation in force production in the lower extremity and postural sway as well as gait variability. Based on their clinical classification of "fallers vs. non-fallers" we found no *linear* relationship between neuromuscular noise and postural sway or gait variability and were unable to confirm our proposed hypothesis of linear association between neuromuscular noise and task variability.

In an attempt to understand the underlying relationships between neuromuscular noise and variability during task performance, the 70 elderly women were then classified based on their levels of neuromuscular noise (force fluctuations in the lower extremity). The results showed that subjects with *nominal levels of neuromuscular noise* throughout the lower extremities exhibited a clear association between levels of force fluctuation and variability during standing as well as walking ($r^2>0.23$), whereas those with *extreme (high as well as low) noise levels* did not. These results indicate that there is a *non-linear* relationship between neuromuscular noise and variability during task output. The results show that in individuals with nominal levels of neuromuscular noise, the variability during both static and dynamic tasks was proportional to the level of intrinsic neuromuscular noise. This observation then poses the question of whether the lack of this relationship in individuals with extreme levels of noise indicates a deficit in the sensori-motor system. Although further research involving approaches to combine unique neuro-physiological parameters needs to be conducted in this area to better understand the relationship between neuromuscular noise, output task variability, and functioning of the sensori-motor system, the subjects with extreme levels of noise did indeed possess lower stride lengths, isometric muscle strengths and walking speeds. The lower levels in all of these physiological and functional parameters suggest that extreme levels of noise during force production in the lower extremities might be associated with functional deficits consistent with reduced gait stability [21,88] and even falling [69,149,150], and could therefore be considered a key neuromuscular deficit in the elderly.

The multi-factorial nature of both the sensorimotor system as well as task complexity that the output task performance depends upon factors such as the recruitment of motor units within a particular muscle [54,59,116,202,208], muscle force-length and force-velocity relationships [201,209,210,211], muscle coordination [212,213,214,215,216,217], sensori-motor feedback quality [218,219,220,221,222], and alternating activation of agonist, synergists and antagonist muscles [29,56,116,208,223,224,225], as well as the requirements of the task itself [202,222,226,227,228,229]. While considerations of many of these factors and their interactions were outside the scope of this work, the assessments undertaken in this study clearly indicate that variability during task performance does provide information regarding not only the level of neuromuscular noise [58,60,61], but also the functioning of the human sensori-motor system. Further confirmation of approaches undertaken as well as the results obtained within this dissertation can be found from studies that have showed:

- A clear association between variability in discharge rates of active motor units and levels of force production [58,60,61,78,168], suggesting that force fluctuations during isometric tasks closely represent neuromuscular noise present in the system.

- Presence of extreme or non-optimal levels of variability during walking has been found to be a fall risk factor [121], suggesting that extreme levels of variability during walking might indicate motor-related pathology. In tasks such as walking or standing, where maintenance of balance is a key component for effective performance, excessive levels of variability could lead the state of the system closer to the limits of ability (stability boundaries during balance tasks, walking etc.). In these cases the sensori-motor system would be required to generate corrective actions. An inability to generate such corrective actions could lead to task failure, and in specific cases, even falls. Although, further research needs to be conducted to better understand any detrimental effects of extremely low levels of variability, it might indicate loss of complexity but also possibly of redundancy within the human sensori-motor system [27,127,128].

- Harris and Wolpert [47] showed that noise is not only an inherent part of neuronal control signals, but also that the magnitude of noise is proportional to that of the neuronal signal. A number of studies have since used empirical models to extend this relationship between signal and noise during task performance [25,30,46,50]. This property of proportionality between signal and noise, within the sensori-motor system adds additional importance to the quantification of the levels of neuromuscular noise. In one of the studies conducted within this dissertation, individuals with extreme levels of noise seem to have regulated the levels of signal (e.g. magnitudes of stride length or walking speed) in order to compensate for the extreme levels of noise within the sensori-motor system. Further support for considering extreme levels of variability as a motor-related deficit was provided by Rosano and co-workers [70]. The authors reported trends suggesting that individuals with extreme levels of temporal gait variability had a greater likelihood of exhibiting vascular deformity in the brain [70].

These investigations suggest that variability during task performance and neuromuscular noise levels are important criteria, and, if properly incorporated within the clinical setting, could provide the basis for early as well as effective identification of specific motor-related pathologies. Further research focusing on the underlying mechanisms need to be conducted in order to not only better understand the functioning of the human sensori-motor system and task performance, but also to establish intra-subject variability as a functional biomarker in clinical settings for early and effective identification of motor-related pathologies, but also for designing rehabilitation programs.

Conclusions and Outlook

While future investigations need to focus on mechanisms related to the levels of noise and their interactions in both the afferent and efferent systems, as well as the underlying associations between intrinsic noise and the quality of task performance, the variability during task performance was shown to be a key parameter for identifying fatigue-, age- and fall-related differences in the sensorimotor system. These results collectively indicate that trial-to-trial variations are sensitive not only to perturbation of intrinsic and extrinsic factors such as visual and surface conditions, but also to stability issues and even fall-related changes. The importance of considering variability (trial-to-trial variations) in task performance has therefore been highlighted as a functional biomarker for motor-related pathologies. When conducted in a standardized manner, these investigations could effectively complement current clinical practice for early and effective identification of individuals with motor-related pathology, designing subject-specific rehabilitation programs, as well as evaluating different therapies. Further translational investigations could provide improved insight into the relationships between variability during task performance and functioning of the human sensori-motor system by incorporating rehabilitation programs focusing on aspects such as physio-, pycho- as well as pharmoco-logical therapies in clinical settings.

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Appendix

Appendix A: Biosketch

Navrag B. Singh

Navrag Singh completed his Masters of Science degree with specialization in Human Factors and Ergonomics in October 2005 from Virginia Polytechnic Institute and State University in Blacksburg, Virginia (USA). At Virginia Tech he was working as a Research assistant at the Industrial Ergonomics and Biomechanics laboratory and was involved in a multi-center project sponsored by Centers of Disease Control, in analyzing the effects of fatigue on postural stability and balance in young and old adults. The research project addressed the issue of fatigue as a factor contributing towards loss of balance incidents in the construction industry.

After finishing his MS, he joined the Liberty Mutual Institute for Safety in Boston, Massachusetts as a Biomechanics Research Assistant. At the institute he worked towards understanding and evaluating the impact of initial lumbar and knee postures, and pre-lift dynamics on low back loading. He was involved in the measurement of lifting trials as well as the development of 3-D inverse dynamics model to analyze low-back and knee joint moments during different lifting conditions. The results are being used to recommend biomechanical adjustments for both pre- and post-lift to reduce the risk of low back injuries. Currently he is working at the Julius Wolff Institute, Charité – Universitätsmedizin, Berlin and is involved in an EU project aimed at understanding and quantification of muscular control, postural stability and gait characteristics among elderly women. The results will be used in determining subject-specific functional metrics for the assessment of fall risk in the clinic, which would further be used in estimating fracture risk among elderly women.

Appendix A: List of publications

Singh NB, König N, Arampatzis A, Heller MO, Taylor WR
Extreme levels of noise constitute a key neuromuscular deficit in the elderly. PLoS ONE: in press

Singh NB, Taylor WR, Madigan M, Nussbaum M
The spectral content of postural sway during quiet stance: influences of age, vision and somatosensory inputs. Journal of Electromyography and Kinesiology 22(1); 131-136, 2012

Hamacher D, **Singh NB**, Van Dieën J, Heller MO, Taylor WR
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Appendix A: Abstracts and posters

Hamacher D, Grabau C, **Singh NB**, Schega L, König N, Taylor WR. Gait variability as a representation of the functionality of the sensorimotor system. Poster presentation, 17th Annual Congress of the ECSS, Belgium 4-7 July, 2012

Singh NB, Hamacher D, König N, Heller MO, Taylor WR. Identifying fall prone elderly individuals in a clinical setting. Podium presentation, 18th Congress of the ESB, 1-4 July 2010, Lisbon, Portugal

Singh NB, König N, Arampatzis A, Heller MO, Taylor WR. Fluctuations during force production play a direct role in the quality of task performance. Podium presentation, 18th Congress of the ESB, 1-4 July 2010, Lisbon, Portugal

Singh NB, König N, Heller MO, Taylor WR. Understanding pathological gait: A holistic approach applied to Parkinson's Disease. Podium presentation, 18th Congress of the ESB, 1-4 July 2010, Lisbon, Portugal

Taylor WR, Damm P, Bergmann G, Rohlmann A, **Singh NB**, Sharankov A, Trepczynski A, Heller MO. Patient-Specific Loading in the Proximal Femur. Workshop Podium Presentation, Orthopaedic Research Society (ORS), San Francisco, 4-8 Feb 2012

Singh NB, Nussbaum M, Madigan M, Taylor WR. The spectral contact of postural sway during quiet stance – influences of age, vision and somatosensory inputs. Podium presentation at the 7. Jahrestagung der Deutschen Gesellschaft für Biomechanik. Murnau, May 2011

Singh NB, Arampatzis A, Duda G, Heller MO, Taylor WR. Effect of localized muscle fatigue on force fluctuations in knee extensors in young adults. Podium presentation at the 17th Congress of the European Society of Biomechanics, Scotland, 5 – 8th July 2010

Singh NB, Arampatzis A, Duda G, Heller MO, Taylor WR. Force fluctuations in the knee extensors: Effect of aging. Symposium der DVS-Sektionen Biomechanik, Sportmotorik und Trainingswissenschaft. Germany, 2nd – 4th Sept 2010

Taylor WR, **Singh NB**, König N, Heller MO. Towards an understanding of subject-specific risk of falls. Podium presentation, IUTAM congress, Leuven, Belgium, 13-15th Sept 2010

Goudakos I, König C, Schöttle P, Taylor WR, **Singh NB**, Pöpplau B, Duda GN, Heller MO. Die Regulation der patellofemoralen Kontaktfläche ist ein essentieller Mechanismus um die physiologische in vivo Biomechanik aufrecht zu erhalten Poster presentation, 23 Kongress der Gesellschaft für Orthopädisch-Traumatologische Sportmedizin, München

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